

**The Effect of Acute Acidosis
on Cardiac Output
and Total Splanchnic Perfusion,
with Special Reference
to The Modification of these
Responses by Some Anaesthetic
Agents**

An Animal Experimental Study



Odense 1982

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TO KRISTA

OLE AND THOMAS

PREFACE

The investigations which form the basis of this thesis were carried out during my appointment as a senior anaesthetist at the Department of Anaesthesiology, Odense University Hospital, and as lecturer in anaesthesia at the Institute of Anaesthesiology, Odense University. I have received considerable help from a number of persons in completing the investigations.

Firstly, I would like to thank Niels Einer-Jensen, D.V.M., Institute of Physiology, Odense University, for his co-operation in the investigations. Despite the fact that he is, by choice, a reproduction physiologist, he willingly and unsparingly accepted the work entailed in co-operating with me in solving anaesthesiological problems. Our team was later supplemented, in the best possible manner, by Tommy Madsen, Medico-engineer, Department of Thoracic Surgery, Odense University Hospital. His theoretical knowledge and practical ability in biological measurements was of invaluable help.

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Prof. Søren Jørgensen, M.D., Department of Anaesthetics, Odense University Hospital, was - many years ago - my instructor in prac-

tical anaesthesia. His great interest in scientific aspects of our profession has been passed on to many pupils. His example has been a source of inspiration for my work on this book.

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I am grateful to the secretaries of the Department of Anaesthetics, Odense University Hospital, for the work they have carried out in typing the various publications and the first edition of the manuscript.

The present manuscript has been compiled during my appointment as professor of anaesthesia at the University of Aarhus and as the senior anaesthetist of the Department of Anaesthesiology, Aarhus University Hospital. I wish to thank my colleagues in the department for their flexibility in planning the many new tasks we have undertaken. This has been an important prerequisite for the completion of this work.

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Last, but not least, I thank my wife and children: Krista, Ole and Thomas who have amiably accepted the fact, that my limited leisure

hours together with them had to play second fiddle to the work involved in the publication of this book.

October 1981

BENT JUHL

THIS DISSERTATION IS BASED ON THE FOLLOWING ARTICLES, TO BE REFERRED TO IN THE TEXT BY THEIR ROMAN NUMERALS

- I Hepatic blood flow and cardiac output during halothane anaesthesia: an animal study. (1974)
B. Juhl & N. Einer-Jensen
Acta anaesth. scand. 18, 114.
- II Hepatic blood flow and cardiac output during Fluoromar^R anaesthesia: an animal study (1976).
B. Juhl & N. Einer-Jensen
Acta anaesth. scand. 20, 271.
- III The effect on the splanchnic blood flow and cardiac output of various carbon dioxide concentrations during Fluoroxene (Fluoromar^R) anaesthesia: an animal study. (1977).
B. Juhl & N. Einer-Jensen
Acta anaesth. scand. 21, 449.
- IV The effect of acute respiratory acidoses on the proportion: total splanchnic perfusion/cardiac output, and the alteration in this proportion by two anaesthetics (1978).
B. Juhl & N. Einer-Jensen
Acta anaesth. scand. 22, 497.
- V The effect of non-carbonic acidosis on total splanchnic perfusion and cardiac output during anaesthesia with O₂-N₂O-barbiturat-relaxan (1979).
B. Juhl, N. Einer-Jensen & T. Madsen
Acta anaesth. scand. 23, 149.

VI The effect of non-carbonic acidosis on total splanchnic perfusion and cardiac output during anaesthesia with O_2 - N_2O -halothane (1979).

B. Juhl, N. Einer-Jensen & T. Madsen.

Acta anaesth. scand. 23, 156.

CONTENTS

<u>CHAPTER 1:</u>	INTRODUCTION AND AIM OF THE PRESENT STUDY	12
<u>CHAPTER 2:</u>	PREVIOUS INVESTIGATIONS	15
2.1.	THE EFFECT OF ACIDOSIS ON THE ISOLATED HEART/ BLOOD VESSELS AND THE INTACT ORGANISM	15
2.2.	THE EFFECT OF CARBONIC ACIDOSIS ON THE SYSTEMIC CIRCULATION DURING ANAESTHESIA	17
2.3.	THE EFFECT OF NON-CARBONIC ACIDOSIS ON THE SYSTEMIC CIRCULATION DURING ANAESTHESIA	19
2.4.	THE AUTONOME NERVOUS SYSTEM AND THE SPLANCHNIC VASCULAR BED	19
2.5.	SPLANCHNIC PERFUSION DURING ANAESTHESIA	22
2.6.	CARBONIC ACIDOSIS AND SPLANCHNIC PERFUSION	23
2.7.	NON-CARBONIC ACIDOSIS AND SPLANCHNIC PERFUSION.	26
<u>CHAPTER 3:</u>	MATERIAL	29
3.1.	THE BODY WEIGHT OF THE DOGS	29
3.2.	RELATION LIVER WEIGHT/BODY WEIGHT	29
<u>CHAPTER 4:</u>	METHODS	30
4.1.	ANAESTHESIA	30
4.1.1.	PREMEDICATION	30
4.1.2.	INDUCTION OF ANAESTHESIA	30
4.1.3.	TYPES OF ANAESTHESIA	31
4.2.	SURGICAL PROCEDURES	32

4.3.	INDUCTION OF ACIDOSIS	33
4.3.1.	CARBONIC	33
4.3.2.	NON-CARBONIC	34
4.3.3.	THE INFLUENCE OF PH ON THE DEPTH OF ANAESTHESIA	34
<u>CHAPTER 5:</u>	MEASUREMENTS	38
5.1.	CARDIAC OUTPUT	38
5.1.1.	DYE-DILUTION	38
5.1.2.	THERMO-DILUTION	40
5.2.	TOTAL SPLANCHNIC PERFUSION	42
5.3.	PRESSURE MEASUREMENTS AND BLOOD SAMPLING	49
<u>CHAPTER 6:</u>	INTERPRETATION OF MEASUREMENTS	51
<u>CHAPTER 7:</u>	RESULTS	54
7.1.	BASIC ANAESTHESIA	54
7.1.1.	CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION	54
7.1.2.	CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION	56
7.1.3.	NON-CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION.	59
7.1.4.	NON-CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION.	62
7.2.	HALOTHANE ANAESTHESIA	63
7.2.1.	CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION	63
7.2.2.	CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION	66

7.2.3.	NON-CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION	68
7.2.4.	NON-CARBONIC ACIDOSIS-SPLANCHNIC PERFUSION	70
7.3.	FLUOROMAR ANAESTHESIA	73
7.3.1.	CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION ,	73
7.3.2.	CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION ,	77
7.4.	SUMMARING THE RESULTS	84
7.5.	CLINICAL ASPECTS	89
SUMMARY		94
DANISH SUMMARY		99
APPENDIX		104
REFERENCES		111

Just as hypercapnia may make it difficult to unravel the changes produced by anesthesia, so anesthesia may complicate the understanding of hypercapnia.

EPSTEIN et al., 1961

CAPTER 1. INTRODUCTION AND AIM OF THE PRESENT STUDY

August Krogh (1912) pioneered the conception that the splanchnic circulation plays an important role in circulatory homeostasis. This has later been confirmed by several investigators, who studied this function, when the circulation is affected by: changes in surrounding temperature (Glaser et al., 1950), work (Wade et al., 1956, Rowell et al., 1974), sudden change from the horizontal to vertical position (Wilkens et al., 1951), pooling of blood in the lower extremities with a negative pressure suit (Rowell et al., 1972), changes in blood volume (Price et al., 1966), acute and prolonged haemorrhagic shock (Reynell et al., 1955) and changes in the circulation after cardiac arrest (Evtushenko, 1975).

The vessels of the splanchnic region participate in circulatory homeostasis in two ways. They represent a large centrally situated capacitance (Greenway & Lister, 1974, Lutt & Greenway, 1976), with a compliance, which is twice the size of the compliance of the remaining circulatory vessels (Mitzner & Goldberg, 1975). Changes in this volume-reservoir will be able to increase or reduce venous return briefly. Under steady-state conditions (cardiac output = venous return) the changes in the regional distribution of the cardiac output are of greater importance (Caldini et al., 1974). These authors also point out that the splanchnic circulation is probably the essential part of the

compartment with a long time-constant (compliance x resistance), which is of importance for the control of venous return by peripheral factors.

The majority of anaesthetic agents have a depressing effect on the circulation, both universally and regionally. The splanchnic perfusion is also affected, and generally a flow reduction is seen. The anaesthesiological aspects of this flow reduction have most frequently been whether it could produce liver hypoxia (Price et al., 1966). On the other hand, the issues in question have rarely been whether these flow changes are of any importance to circulatory homeostasis during anaesthesia. It can be deducted from the literature that none of the anaesthetic agents employed today produce changes in the splanchnic perfusion which in themselves can be presumed to be of importance with regard to universal circulatory homeostasis under normal conditions. In addition to being depressive on the circulation, the anaesthetic agents also produce respiratory depression. Both effects promote the development of acidosis: non-carbonic and carbonic acidosis. Both types of acidosis affect the circulation in two ways: partly peripheral, direct depressive effect on the heart and blood vessels and partly a central stimulatory effect on the autonomic nervous system. This stimulation of the sympathetic nervous system predominates, even though acidosis also stimulates the parasympathetic nervous system. Thus acute acidosis brings about many reactions, and several of these, as will be obvious from the above, oppose each other. Changes in the perfusion of the splanchnic bed are, as mentioned earlier, of great importance with regard to circulatory homeostasis during other forms of circulatory stress. It is probable that this is

also the case during the circulatory adaption to acute acidosis.

The aim of the present study has been to investigate the part played by the splanchnic perfusion in the changes which take place in the systemic circulation as a reaction to acute acidosis during anaesthesia, with special emphasis on the influence of the anaesthesia on the triggered reactions.

CHAPTER 2: PREVIOUS INVESTIGATIONS

2.1. THE EFFECT OF ACIDOSIS ON THE ISOLATED HEART/BLOOD VESSELS AND THE INTACT ORGANISM

The contractility of in vitro isolated atrial and ventricular muscles is depressed to the same extent by "respiratory" and "metabolic" acidosis (Cingolani et al., 1975). Acidosis (increasing $p\text{CO}_2$ or decreasing pH) of the perfusion solution of an isolated perfused heart causes a reduction in the heart rate and contractility, as well as a rise in the coronary blood flow (Price & Helrich, 1955, McElroy et al., 1958). The changes probably result from changes in intracellular pH (Wang & Katz, 1965) If the intracellular pH is kept constant during rising $p\text{CO}_2$, then no change can be demonstrated (Ng et al., 1967). Acidosis causes a reduction in the tone of isolated vessels (Wagner et al., 1975).

In the intact organism, these reactions to acidosis are modified by the effect of acidosis on the central and autonome nervous systems. The vasomotoric centre is stimulated directly and via chemoreceptors (Tenny, 1960). With regard to the autonome nervous system, the reaction is by far a sympathetic stimulation. Under anaesthesia, hypercapnia produces increased activity in the pre-ganglion area in the cervical sympathetic trunk (Skovsted et al., 1972), and the plasma concentrations of adrenaline and noradrenaline rise during both carbonic and non-carbonic acidosis (Morris & Millar, 1962 a, b). The effect of acidosis on the blood flow through the individual organs will therefore also be dependent on to what extent the circulatory system in question is under neurogenic con-

trol and to what extent they contain receptors for sympathetic and parasympathetic transmitter substances.

The local dilatating effect on blood vessels of hypercapnia predominates in the vessels of the brain (Kety & Schmidt, 1948), as well as in the coronary vessels (Kittle et al., 1965, Föex, 1980). The vessels of the kidney, on the other hand, are dominated by sympathetic stimulation (Kittle et al., 1965) and they contract during hypercapnia. In the striated muscle, the contracting and dilatating effect counter balance each other and the vascular resistance remains unchanged (Richardson et al., 1961). The blood vessels of the intestines are dilatated by hypercapnia (McGinn et al., 1967).

The infusion of HCl-solution with variations in blood pH down to 7.0 does not change the resistance in the coronary vessels (Kittle et al., 1965), or in the vessels of the brain (Harper & Bell, 1963). The vascular resistance in the kidneys is not changed (Simmons & Oliver, 1965) or rises slightly (Kittle et al., 1965). The vascular resistance in the muscles and skin falls slightly (Deal et al., 1954). The resistance in the intestinal vessels remains unchanged (McGinn et al., 1967).

Pulmonary vascular resistance increases after both carbonic and non-carbonic acidosis (Bergofsky et al., 1962, Barer et al., 1967).

2.2.

THE EFFECT OF CARBONIC ACIDOSIS ON THE SYSTEMIC
CIRCULATION DURING ANAESTHESIA

Previous investigations on this subject have demonstrated qualitative uniform but quantitative slightly differing results. Experimental studies on dogs have shown an increase in cardiac output and a fall in peripheral resistance, while the pressure in the right atrium and aorta remain unchanged. The effect on the heart rate has been more inconsistent. These observations have been made during anaesthesia with barbiturates (Kittle et al., 1965, Andersen & Mouritzen, 1966, Manley et al., 1964, Morgan et al., 1967, Wendling et al., 1967 and Carson et al., 1965), light halothane anaesthesia (Tomlin et al., 1966), fluoromar anaesthesia (Stoyka et al., 1970) and anaesthesia with diethylether (Sodipo et al., 1975). Clinical investigations have given similar results during anaesthesia with halothane, fluoromar and cyclopropane (Cullen et al., 1971).

The effect of a certain change in $p\text{CO}_2$ or a corresponding change in pH, for instance, cardiac output during differing forms of anaesthesia are not comparable in the above mentioned animal investigations. A comparison should be carried out at analgetic equipotence, but it has not been possible to define analgetic potency of the drugs used in intravenous anaesthesia (Dundee & Wyant, 1974) in the same manner as has been possible with regard to inhalation anaesthetics (Eger et al., 1965). In addition, the analgetic effect of anaesthetic agents changes due to changes in the equilibrium of acid-base (Eisele et al., 1967) and furthermore these changes are only partly known with regard to some anaesthetic agents. Anaesthetic equipotence is therefore difficult to maintain

during the induction of acidosis. However, with this reservation, the above mentioned investigation of Cullen et al. (1971) shows that a rise in cardiac output from a given change in $p\text{CO}_2$ was least during anaesthesia with halothane, greater during fluoromar and greatest during cyclopropane. This rank is in agreement with the three anaesthetic agents own sympathetic stimulating effect, which also increases in the mentioned sequence. It is known that the sympathico-adrenergic response triggered by the individual anaesthetic agent is well related to the haemodynamic conditions during anaesthesia with the agent in question (Price et al., 1959).

During anaesthesia with barbiturates, cardiac output does not change significantly during intermittent positive pressure ventilation (IPPV) from that measured during spontaneous breathing, when normocapnia is retained with a tidal volume of 15 ml/kg b.w. (Cassidy et al., 1978). On the other hand, the cardiac output changes during mechanical hypo- and hyperventilation. The changes brought about by IPPV are dependent on 1) the increase in the intrathoracical pressure, 2) the change in p_{aCO_2} and 3) the circulating blood volume. If the intrathoracical pressure is increased, the cardiac output is reduced, because the venous return is reduced. (Morgan et al., 1966). This effect of IPPV is enhanced by hypovolaemia and peripheral vesseldilatation (Morgan et al., 1969). Carbonic acidosis and increased intrathoracical pressure thus have not only opposite effects on cardiac output, but the effect of the increased intrathoracical pressure is accentuated by hypercapnia (Morgan et al., 1967).

2.3. THE EFFECT OF NON-CARBONIC ACIDOSIS ON THE SYSTEMIC CIRCULATION DURING ANAESTHESIA

Investigations on this subject have given varying results. This is probably related to the various methods used to induce this acidosis. Non-carbonic acidosis has been induced with brief, graduated hypoxia, infusion of inorganic acid (hydrochloric acid) and organic acid (lactic acid). Carson et al., (1965) have demonstrated that the latter method brings about "variable and inconstant" changes, while the two other methods cause uniform comparable changes. During anaesthesia with barbiturates, hydrochloric acid infusion brings about a slight fall in cardiac output, a rise in peripheral resistance, as well as a falling heart rate, but the pressure in the right atrium and aorta remain unchanged (Kittle et al., 1965, Smith & Corbascio, 1966). Semilar observations have been made during anaesthesia with halothane (Tomlin et al., 1966) and diethyl-ether (Sodipo et al., 1975).

2.4. THE AUTONOME NERVOUS SYSTEM AND THE SPLANCHNIC VASCULAR BED

The blood vessels of the splanchnic area are followed by a large number of nerves from the autonome nervous system (Kuntz, 1953). The neurogenic regulation of the hepatic vessels appears to occur entirely through the sympathetic nerves (Kuntz, 1953, Andrews et al., 1956). Parasympathetic nerves of any importance for the innervation of the spleen have not been demonstrated (Utterback, 1944, Green et al., 1960) and the mesenteric vessels have no cholinergic nerves (Owman, 1979).

The adrenergic receptors in the arterioles of the systemic circulation can be classified according to the response to adrenergic stimuli into α and β receptors (Ahlquist, 1948). These receptors have been demonstrated in the arterioles of the spleen and small intestine (Ross, 1967, a, b, Green et al., 1960), and in the hepatic artery (Geumei & Mahfouz, 1968, Greenway & Lawson, 1969), as well as in the systemic venous bed (Kaiser et al., 1964). In contrast to the opposing actions of these receptors in the arterial bed, stimulation of either α or β receptors produces venoconstriction on the entire systemic capacitance bed (Kaiser et al., 1964). The number and distribution of these receptors are not only species and age dependent but also vary from one organ to another (Bevan et al., 1980). In agreement with this the reaction to adrenergic agents injected locally into the afferent vessels of the organ, differs from one organ to another. Both adrenaline and noradrenaline cause contraction of the splanchnic vessels. Noradrenaline has a slightly more pronounced effect than adrenaline and the relative sensitivity to adrenergic constrictive substances is, in order of decreasing sensitivity: mesenteric artery bed, hepatic artery bed, and portal venous bed (Green et al., 1959).

The vasoconstrictory effect mediated via splanchnic nerve has also a stronger effect on the mesenteric vessels than on the hepatic artery and portal vein.

β receptors, which on stimulation produce blood vessel dilatation, appear to show the same distribution pattern within the splanchnic area. β dilatatory response has thus been demonstrated in the superior mesenteric artery (Green et al., 1955, Deal & Green, 1956, Wilson

et al., 1977), and in the lienal artery (Ross, 1967 b), whereas Green et al. (1959) were unable to find indication of this reaction in the vessels of the liver. Later investigations have, as mentioned (Geumei & Mahfouz, 1968, Greenway & Lawson, 1969) demonstrated β receptors in the hepatic artery, but not in the portal vein.

The adrenergic receptors are depressed by acidosis. α receptors are in this respect less sensitive, i.e. are depressed to a lesser extent than β receptors, during carbonic (Wood et al., 1962) and non-carbonic acidosis (Wagner et al., 1977).

The relation between splanchnic perfusion and perfusion pressure is complex. Total splanchnic perfusion, Mitzner's "hepatic common outflow" (1974 a) does not reveal autoregulation. The hepatic artery, on the other hand, shows autoregulation (Hanson & Johnson, 1966). An intact portal flow is of importance for this reaction. If the portal flow is shunted, the arterial autoregulation is seen less frequently. The portal flow itself does not demonstrate autoregulation. Teleologically this seems acceptable, when the flow in the portal vein "is determined" by the other intra-abdominal organs. On the other hand, the portal resistance (portal pressure) does have considerable influence on the preportal resistance, and thus has a very important influence on total liver perfusion (Price et al., 1967, Mitzner, 1974 b).

The flow in the hepatic artery changes reciprocally to flow changes in the portal vein (Thernberg & Butcher, 1965, Hanson & Johnson, 1966, Kock et al., 1972). The opposite relation does not occur.

If the flow in the hepatic artery is reduced, the portal flow remains unchanged or falls slightly.

Blocking of the α and β receptors does not abolish the autoregulation in the hepatic artery, nor the changes in flow in the hepatic artery, secondary to changes in portal flow (Hanson, 1973, Hirsch et al., 1976, Ulrich, 1977). The last mentioned reaction is also present during induced hypotension with sodium nitroprusside (Gelman & Ernst, 1978).

2.5. SPLANCHNIC PERFUSION DURING ANAESTHESIA

Animal experiments have demonstrated that the majority of anaesthetic agents which are employed clinically reduce the splanchnic perfusion. An exception to this is light ether anaesthesia, which slightly increases the flow (Galindo, 1965, b) and light anaesthesia with barbiturates, which does not change the flow (Everingham et al. 1959), or reduces it slightly (Ahlgren et al., 1978, a). On the other hand, a more pronounced reduction in flow has been demonstrated during anaesthesia with halothane (Galindo, 1965 b, Irestedt, 1978, Ahlgren et al., 1978, b) cyclopropane and chloroform (Galindo, 1965, b) enflurane and neuroleptic anaesthesia (Irestedt, 1978).

Clinical investigations have also demonstrated a reduction in flow during anaesthesia with halothane (Epstein et al., 1966), cyclopropane (Price et al., 1965) and methoxyflurane (Libonati et al., 1973) as well as during high (T_5) spinal and epidural analgesia (Müller et al., 1952, Kennedy et al., 1970, 1971). According to the above mentioned investigations, the reduction in splanchnic perfusion is

60% during anaesthesia with chloroform, 40-50% during halothane, 40-50% during cyclopropane, 30-40% during enflurane, 25% during neuroleptic anaesthesia, 15% during barbiturate anaesthesia and 23% during spinal analgesia.

The splanchnic perfusion is reduced by various causes. Cyclopropane reduces blood flow by increasing regional vascular resistance, halothane does so by reducing systemic arterial pressure (Galindo, 1965 b, Price et al., 1965). The reduction of the flow during spinal analgesia results from a reduction in perfusion pressure also; cardiac output and circulatory resistance in the splanchnic area remain unchanged (Kennedy et al., 1970). During epidural analgesia, the flow, on the other hand, is reduced by an increased regional vascular resistance (Kennedy et al., 1971).

2.6. CARBONIC ACIDOSIS AND SPLANCHNIC PERFUSION

In the isolated and artificially perfused superior mesenteric artery, the vessel tone is reduced when the perfusion solution is made hypercapnic (Rogers et al., 1965). Isolated and artificially perfused pieces of the mesenteric vein, on the other hand, are not changed with regard to tone under the same conditions (Gollwitzer-Meier & Bohn, 1930). If the nerve supply to the artificially perfused piece of mesenteric vessel is intact, universal hypercapnia (CO_2 -breathing) produces, via the central nervous system (the vasomotor centre) a strong contraction of the mesenteric vein (Gollwitzer-Meier & Bohn, 1930, Alexander, 1954), but only a weak contraction of the mesenteric artery (Mohamed & Bean, 1951). The combined effect of local vasodilatation of carbon dioxide and its

sympathetically mediated vasoconstriction is thus the same in the mesenteric circulation as in the entire systemic circulation: the direct vasodilatation predominates in the arterioles, whereas the centrally triggered vasoconstriction dominates in the veins (Braunwald et al., 1965). A rise in the blood catecholamines may accentuate venous constriction, but is unable to counteract the carbon dioxide dilatating effect on the arterioles (Roger et al., 1965). Thus in the intact, anaesthetized animal, the immediate effect of hypercapnia is an increased flow in the superior mesenteric artery (Brinckner et al., 1956). This change is not related to an eventual rise in the arterial blood pressure. It is also seen when the perfusion pressure is kept constant during hypercapnia (McGinn et al., 1967).

Carbonic acidosis also dilatates the arterioles of the spleen, but at the same time the central stimulation and the increased concentration of catecholamines in the blood cause a strong contraction of the spleen (Ramlo & Brown, 1959). After prolonged hypercapnia (20 minutes) the flow in the splenic vein is of the same magnitude as under normocapnia (Hughes et al., 1979).

The immediate reaction (2-3 minutes) of the preportal vascular bed to acute hypercapnia is thus characterized by a reduced resistance in the resistance vessels and a reduced capacity in the capacitance vessels. The immediate effect of this is a rise in the portal flow (Scholtholt & Shiraishi, 1970, Hughes et al., 1979). One would expect that the contribution of the capacitance vessels to this increased flow would decrease with prolonged hypercapnia. Hughes et al., (1979) found, in agreement with this, that the portal flow

after 20 minutes of hypercapnia was almost the same as before exposure to carbonic acidosis, when $p_{aCO_2} < 85$ mm Hg. Only with a p_{aCO_2} higher than this was the portal flow still increased after 20 minutes. The portal circulation's own reaction to hypercapnia contributes to the flow reduction. Universal hypercapnia brings about a rise in pressure in the portal vein (McGinn et al., 1967, Scholtholt & Shiraishi, 1970, Hughes et al., 1979) and this increase in pressure cannot, as suggested by Scholtholt & Shiraishi (1970) be explained from the increased portal flow only. The pressure is still increased after 20 minutes of hypercapnia at a time when the portal flow is reduced (Hughes et al., 1979). The portal vein's own reaction to hypercapnia contributes to the rise in pressure. If hypercapnia is induced locally in the portal vein, without systemic hypercapnia occurring at the same time, then the resistance increases in the portal vein, the portal flow falls and the portal pressure rises (Gelman & Ernst, 1977).

In the same manner as with the other arteries, the effect of carbon dioxide on the hepatic artery is a combination of direct vasodilatation and sympathetically mediated vasoconstriction. The dilatation also dominates in the hepatic artery, and the flow rises when the animal breaths carbon dioxide (Galindo, 1965 a). A pronounced rise has been demonstrated following inspiration of 20% CO_2 (Cohn & Kountz, 1964). The rise in arterial flow can also be fairly small (7.6%) as compared to the very pronounced rise in the portal flow (42.8%), which is produced by carbonic acidosis at $p_{aCO_2} = 65$ mm Hg (Scholtholt & Shiraishi, 1970). One investigation (Hughes et al., 1979) has shown that the flow in the hepatic artery is reduced by hypercapnia. In that investigation, the flow in the

hepatic artery was lowest at the same time as the flow in the portal vein was at its highest. When the portal flow after 20 minutes of hypercapnia decreases, the flow in the hepatic artery increases. However, it did not reach the level of the flow under normocapnia. The somewhat differing results, with regard to the effect of hypercapnia on the flow in the hepatic artery, thus cannot be explained solely from the difference in the degree of acidosis and rapidity with which the acidosis was induced. The flow in the hepatic artery is also inversely related to portal blood flow during hypercapnia (Gelman & Ernst, 1977).

The total effect of hypercapnia on the total splanchnic perfusion is, according to the above mentioned investigations, probably an increased blood flow. Clinical investigations, however, show that anaesthesia can change this reaction. During anaesthesia with barbiturates- O_2/N_2O , hypercapnia produces a reduction in the blood volume in the splanchnic area and an increased vascular resistance (Epstein et al., 1961). These changes do not necessary result in flow reduction but both falling, unchanged and rising blood flows have been demonstrated, depending upon the behaviour of the arterial pressure. During clinical anaesthesia with halothane (Epstein et al., 1966), hypercapnia produces an increased blood volume in the splanchnic bed, a reduction in vascular resistance and an increased blood flow.

2.7. NON-CARBONIC ACIDOSIS AND SPLANCHNIC PERFUSION

Intravenous infusion of hydrochloric acid produces no change in flow in the superior mesenteric artery, as long as the perfusion

pressure is kept constant (McGinn et al., 1967). Isolated, perfused mesenteric veins do not change tone when the hydrogen ion concentration in the perfusion solution is increased (Gollwitzer-Meier & Bohn, 1930). Whereas the injection of small quantities of weak acid into the portal vein produce the same reaction as local hypercapnia: an increase in portal pressure and portal venular resistance and a decrease in portal blood flow (Gelman & Ernst, 1977). The effect of non-carbonic acidosis on total splanchnic perfusion has not been studied.

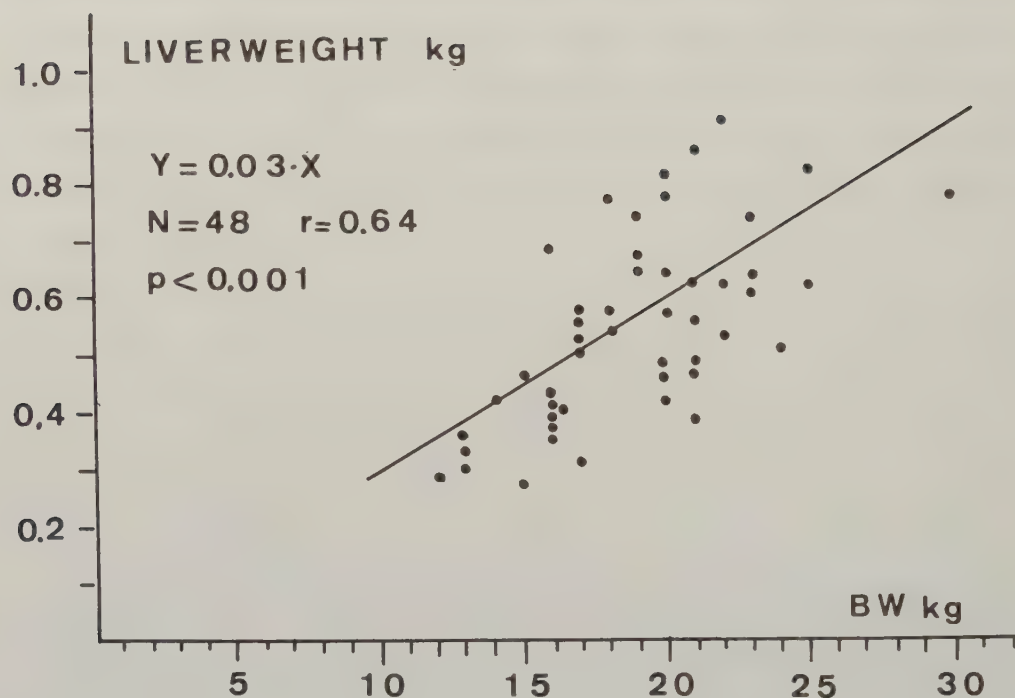


FIGURE 1

THE RELATED VALUES OF BODY WEIGHT AND LIVER WEIGHT FROM 48 DOGS USED IN THE STUDIES I TO VI.

CHAPTER 3: MATERIAL

3.1. THE BODY WEIGHT OF THE DOGS

A total of 48 were used in the individual studies as stated below:

(I)	8 Mongrels	b.w.	17-30 kg	$\bar{x}$: 20.8 kg
(II)	8 Mongrels	b.w.	16-24 kg	$\bar{x}$: 20.1 kg
(III)	7 Beagles	b.w.	13-20 kg	$\bar{x}$: 16.5 kg
(IV)	8 Mongrels	b.w.	12-23 kg	$\bar{x}$: 17.0 kg
	4 Mongrels	b.w.	16-21 kg	$\bar{x}$: 18.5 kg
(V)	7 Saluki	b.w.	16-21 kg	$\bar{x}$: 17.7 kg
(VI)	6 Saluki	b.w.	17-22 kg	$\bar{x}$: 19.8 kg

The body weight and liver weight of the animals are normally distributed. The average body weight is 18,91 kg and the average liver weight 0.55 kg.

3.2. RELATION LIVER WEIGHT/BODY WEIGHT

Liver weight is used in the calculation of total liver flow (total splanchnic perfusion) and as the relation between total splanchnic perfusion and cardiac output is studied, the relation liver weight/body weight is important. This relationship is shown as a scatter plot in figure 1.

The regression equation for the scatter plot shown is: liver weight (kg) = $0.03 \times$ body weight (kg). The line goes through (0,0) and $r = 0.64$, $N = 48$, $p < 0.001$. The average of 30 grams liver weight

per kg body weight is identical to that demonstrated by others (Greenway & Stark, 1971).

As can be seen, the points are relatively scattered round the line. This is in all probability not explained by the race differences. The average relation 30 g liver per kilo b.w. is also found in other species: cats (33 g/kg b.w.), man (30 g/kg b.w.). The scatter might be an expression of the very different nutritional state of the various animals.

CHAPTER 4: METHODS

4.1. ANAESTHESIA

4.1.1. PREMEDICATION

The premedication was 10 mg pethidine per kg b.w. subcutaneously 1 hour prior to the start of the investigation. The animals were fasted from the night before, but permitted water ad libitum.

4.1.2 INDUCTION OF ANAESTHESIA

The animals were anaesthetized with sodium mebumal (NFN) 25 mg per kg b.w. injected intravenously through a plastic cannula (Venflon) into a vein in a front leg. They were paralyzed with 80 mg gallamoni jodidum i.v. and tracheal intubated using a Rüschi tube with cuff. The animals were placed in the supine position by means of a "crib" and fixation of the legs by gauze. Mechanical positive pressure ventilation was employed in all investigations. In study I, this was carried out with a Bird ventilator Mark 4 in connection with

a circle system with absorber. The vapourizer fluotec Mark 2 was positioned on the anaesthetic apparatus outside the circle system. In studies II-VI a Harward piston-pump was used. This respirator was connected to the anaesthetic machine via a reservoir bag. A fluotec Mark 2 was re-calibrated for fluoromar administration. A capnograph (Bechman LBI in study I and Godart in studies II-VI) was connected to a side branch of the tube connection for continuous registration of end tidal CO_2 . This was only used for the immediate adjustment and continuous control of ventilation. Oxygen and nitrous oxide were administered from the rotametre of the anaesthetic machine. The inspiratory oxygen content has been selected within the range 33 to 50%, depending on the type of ventilation used. The requirement was that hypoventilation (II,III) and the induced rebreathing (IV) should not produce hypoxaemia.

4.1.3. TYPES OF ANAESTHESIA

Premedication, mebumal natrium and gallamoni jodidium in combination with $\text{O}_2/\text{N}_2\text{O}$ have been termed basic anaesthesia. It has been employed in all the investigations for the induction of anaesthesia and during preparation of the animals, test measurements and calibrations. This procedure took, on average, approximately one hour. The basic anaesthesia has thus been the initial anaesthesia for the investigations in which halothane was later added to the inspiratory air (I, IV and VI) or fluoromar (II and III). In other investigations (IV and V) the basic anaesthesia was continued using refractory doses of mebumal natrium at the same time as carbonic (IV) and non-carbonic acidosis (V) were induced.

The stated concentrations of halothane and fluoromar are percentages in the inspiratory air (dial setting on the vapourizer).

4.2. SURGICAL PROCEDURES

In investigations I to IV, two catheters were introduced via the femoral vein and artery after cut-down of approximately 2-3 cm in length in the inguinal regions. The venous catheter was advanced to the right atrium, evaluated from the pressure curve, and the tip of the other catheter was placed in the thoracic aorta, estimated from the length of the inserted part of the catheter.

In investigations V and VI, the venous catheter was only introduced to the middle of the inferior vena cava, and this was employed for the HCl-infusion. In these two studies, a Swan-Ganz catheter was introduced via the other femoral vein (a few times through the external jugular vein) and floated to the pulmonary artery (evaluated from the pressure curve). The proximal hole of this catheter was used for the registration of right atrial pressure.

Microlaparotomy was carried out. The incision, 4-5 cm in length, was made in linea alba, between the umbilicus and symphysis. A short piece of the small intestine was withdrawn. A thin plastic catheter was introduced into the portal vein via one of the peripheral mesenteric veins by means of the Seldinger technique. The correct positioning of this catheter was controlled at the end of the experiment when the liver was removed. The other end of the catheter was connected to a three-way stop-cock and brought out via the incision, which was then sutured in the usual manner.

The body temperature of the animal was maintained at a constant level by covering and by mean of a servo-controlled heating lamp with the input signal from a needle shaped thermister in the pectoral muscle.

Isotonic saline was administered intravenously at a rate of 5 ml per kg/hour during the experiment.

4.3. INDUCTION OF ACIDOSIS

4.3.1. CARBONIC

Investigation I: Primary different adjustment with hypo, normo and hyperventilation for the individual animals. During the increasing concentrations of halothane, ventilation was changed with the intention of obtaining normoventilation in all the animals.

Investigation II: Adjustment to normoventilation for all the animals and without changing the ventilation, increasing amounts of fluoromar administered.

Investigation III: Half of the animals were hypoventilated and the other half hyperventilated during step-wise increases in fluoromar concentration up to 6%. The type of ventilation was then changed between the groups, from hypo to hyperventilation and vice versa. The fluoromar concentration was then reduced step-wise to zero.

Investigation IV: Primary adjustment for all animals to slight hyperventilation (normal pH) without any change in tidal volume, carbonic acidosis was induced by rebreathing in an increased dead

space of the apparatus; at arterial pH of approximately 7.0, the anaesthesia was supplemented with halothane 1% and normoventilation was then reestablished by removal of the previously added dead space.

4.3.2. NON-CARBONIC

Investigation V: Primary adjustment to slight hyperventilation for all animals (normal arterial pH). During unchanged basic anaesthesia and ventilation, non-carbonic acidosis was induced to arterial pH of approximately 7.0 by means of an i.v. infusion of HCl-solution 0.3 n.

Investigation VI: Primary adjustment to slight hyperventilation for all animals (normal arterial pH). During anaesthesia with $\frac{1}{2}$ % halothane and unchanged ventilation, non-carbonic acidosis was induced to arterial pH of approximately 7.0 by the i.v. infusion of HCl-solution 0.3 n.

4.3.3. THE INFLUENCE OF PH ON THE DEPTH OF ANAESTHESIA

Inhalation anaesthetics: The analgetic potency of inhalation anaesthetic is standardized by the term MAC, i.e. the Minimum Alveolar Concentration of the anaesthetic agent necessary to prevent greater muscle movement as a reaction to painful stimuli in 50% of the tests (Eger et al., 1965).

The other effects of an anaesthetic, including those on the circulation, are often compared at analgetic equipotency (Merkel & Eger,

1963). The potency of an inhalation anaesthetic is independent of the duration of anaesthesia, but is among other things, dependent on the temperature. Following a decrease in body temperature from 38 to 28° C, the MAC for halothane falls by 50%, and for cyclopropane by 25%. The small variations (1 to 2° C) observed in these investigations (I-VI) are therefore without influence on the depth of anaesthesia.

MAC also changes with changes in the acid-base status (Eisele et al., 1967). A p_{aCO_2} variation from 15 to 95 mm Hg (corresponding to arterial pH 7.6 and 7.10, respectively) produced no changes in MAC in dogs. CO_2 has a progressive narcotic effect with concentrations above 95 mm Hg. The animals were anaesthetized by the CO_2 alone at a p_{aCO_2} value of 245 mm Hg (i.e. halothane had a MAC value of 0). Induced non-carbonic acidosis (0.3 n hydrochloric acid via a stomach tube) only changed the MAC of halothane slightly. With arterial pH values down to 6.90 the most frequent finding was a slight fall, on average between 10 and 15%.

Premedication and intravenous anaesthetics: It is not possible to employ an analogous term to MAC with regard to the premedication and intravenous anaesthetics (Dundee & Wyant, 1974). Most frequently they are employed, as here, in doses per kg b.w. (pethidine and nembutal) or as a constant dosage (gallamine). Many, at present partly unknown, factors influence the concentration of these compounds in the blood and tissue (Dundee & Wyant, 1974). In respect of the distribution and further fate in the organism of intravenous anaesthetics, the three most important factors are: protein binding, fat solubility and ionization.

Pethidine: Acidosis changes the distribution coefficient of pethidine. Microelectrometric titration in a two-phase system (lipid/water) has shown a fall in the coefficient of distribution of approximately 48% with a pH variation from 7.4 to 7.1 (Benson et al., 1976). The amount of the compound passing the blood-brain barrier is related to the coefficient of distribution. Induction of acidosis therefore represents a decreasing effect of pethidine.

Barbiturates: The majority of barbiturates have a maximum protein binding at pH = 8.0, decreasing with changes in both directions. At pH 7.4, the fraction of pentobarbitol bound to the plasma proteins is 0.35 (Goldbaum & Smith, 1954). The protein binding decreases with a falling pH. The non-protein bound, non-ionized fraction of the drug is lipid soluble and therefore pharmacologically active. The relationship between non-ionized and ionized fraction is pH dependent.

If carbonic acidosis is induced (pH down to 6.8), the plasma concentration of a barbiturate falls by 40% (Brodie et al., 1950, Rayburn et al., 1953). The tissue concentration rises accordingly. On return to normocapnia, the initial plasma values are almost reached once again. Carbonic acidosis has the same effect on the distribution of phenobarbitone (Waddell & Butler, 1957).

Gallamoni jodidum: The neuromuscular blocking properties of gallamine are affected by acid-base changes. Carbonic acidosis counteracts the neuromuscular effect of gallamine (Payne, 1958).

The circulatory effect of gallamine (rising heart rate, rising

cardiac output and unchanged stroke volume) may possibly be modified by changes in the acid-base status. The influence of carbonic acidosis on the effect of gallamine on the circulation has been studied by Eriksen et al., (1977) on dogs, where the anaesthesia was induced with thiopental and continued with halothane- O_2 - N_2O . It was demonstrated that gallamine does not effect the inotropic state of the heart as evaluated from dp/dt max. In this respect there was no difference between the hypo and hypercapnic groups. The heart rate rose in both groups by 20 - 25%, slightly more in the hypocapnic than in the hypercapnic group. The most pronounced increase in cardiac output was seen in the hypocapnic group (30%). But only at 1 and 5 minutes were these different from those in the hypercapnic group. The mean pressure in the aorta, central venous pressure and the resistance in the systemic circulation were unchanged.

Conclusion: Acidosis in the pH interval employed may reduce the effect of premedication and increase the effect of the induction agent and the inhalation anaesthetic.

In respect of inhalation anaesthesia, the acidosis produces an increase in the depth of anaesthesia of approximately 10%.

CHAPTER 5: MEASUREMENTS

5.1. CARDIAC OUTPUT

The cardiac output was measured in investigations I to VI by the indicator dilution method (Stewart-Hamilton method). In the first four investigations (I-IV) using cardio-green as the indicator (dye-dilution) and in the last two studies (V-VI) with cold isotonic saline as the indicator (thermo-dilution) (Fegler, 1954, Ganz & Swan, 1972). The principle of both methods is that a known amount of indicator is injected as a bolus and registration downstream of the concentration variation as a function of time.

5.1.1. DYE-DILUTION

Static calibration was employed at the start of the investigation, and the test solution was produced from the dog's own blood, with a concentration of 5 mg cardio-green^R per litre. Cardiac output was measured with a bolus injection into the right atrium of the cardio-green 2.5 mg or 5 mg in isotonic saline, 1 ml or 2 ml respectively, were used. The catheter was immediately flushed with 10 ml of isotonic saline. The injection was carried out with a syringe which had been calibrated by weighing. The concentration-time curve was registered by sampling from the thoracic aorta (0.4 ml/s) by means of an accurate motor operated glass syringe (Kipp) and a Water's cuvette densitometer. The densitometer was connected to a recorder with a paper speed of 5 mm per second and an amplification, where the concentration 1 mg cardio-green per litre produced a deflection on the paper of 6-7 mm. The dye recir-

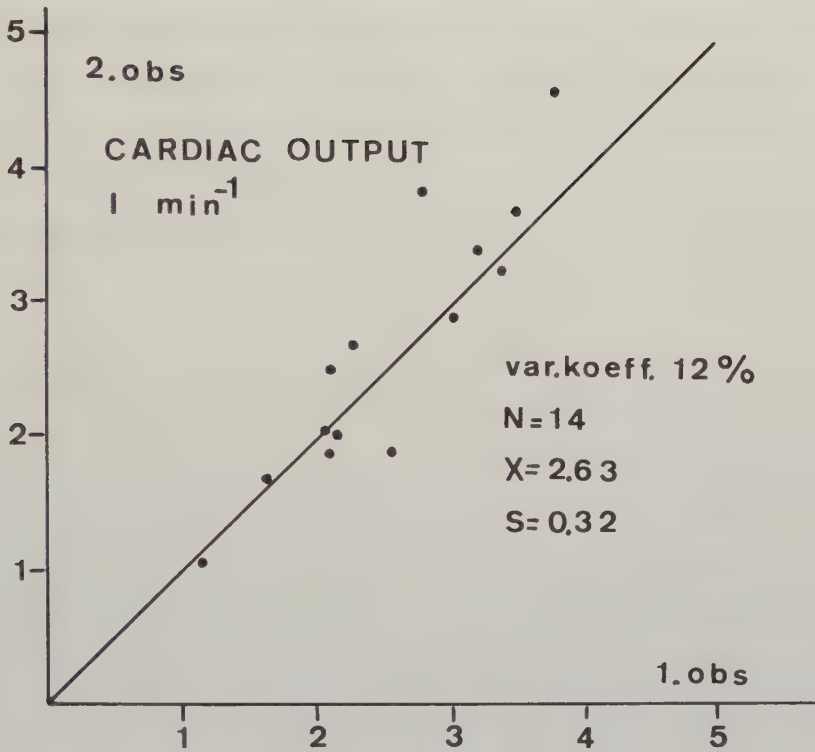


FIGURE 2

DOUBLE DETERMINATIONS OF CARDIAC OUTPUT USING THE
DYE-DILUTION TECHNIQUE.

culates before being eliminated and the curve is bimodal with a primary curve for the first passage and a secondary curve for the first re-circulation. The down slope of the primary curve is an exponential decay. The effect of re-circulation is ignored by re-plotting the down slope on a semi-logarithmic scale and extrapolating the straight line to the intercept with the x-axis. The extrapolated part represents the constructed course of the down slope provided re-circulation has not occurred. The concentration-time curve is read at intervals of one second and calculation of the area beneath the curve and cardiac output were carried out by means of an IBM 1130 computer.

The cardiac output (CO) was calculated using the formula $CO = (I \times 60) / A$, where I is the injected amount of indicator in mg and A the area beneath the curve during the first passage in $mg \text{ lt}^{-1} \text{ sec}$.

In order to test the precision of the method, 14 double determinations were carried out, i.e. two measurements carried out with as short a time interval as possible, and without any change being made in the set-up. The results can be seen from fig. 2, where the first observation is shown on the x-axis and the second observation on the y-axis. The range is from approximately 1 to 4 litres per minute, and the coefficient of variation 12%. The measuring method is not dependent on pH variations (Bloomfield, 1974).

5.1.2. THERMO-DILUTION

Measurement of the cardiac output by means of this method has

been carried out using a Swan-Ganz catheter model 93-122-7F, introduced via the femoral vein (a few times via the external jugular vein) and positioned with the tip in the main branch of the pulmonary artery (as evaluated from the pressure curve). A bolus injection of 6 ml of isotonic saline 0°C was used for each determination of cardiac output; as soon as the plunger was at the bottom, immediate retraction with withdrawal of 1 ml of water, corresponding to the volume of the catheter (Ganz & Swan, 1972). Five ml were employed as the volume in the calculation. The temperature changes were registered on a recorder. The calculation of the cardiac output was carried out using the formula

$$\text{CO} = \frac{q_i \times c_i}{q_b \times c_b} \times 0.747 \times (T_b - T_i) \times \frac{\text{vol}_{\text{inj}} \times 60}{\text{area}}$$

q is the specific gravity and c the specific heat for the injectate (i) and blood (b), respectively. If isotonic saline is used and the haematocrit of the blood varies within the range 35 - 56, then this fraction has a value of 1.08 (Ganz & Swan, 1972). The injectate is heated during its passage through the catheter and the temperature of the injectate when it leaves the catheter is not known. It is possible to make correction for this. The correction factor will be dependent on the volume and temperature of the injectate and to a lesser degree on the intravascular part of the catheter. When 5 ml of isotonic saline are used, the correction factor recommended by the manufacturer is 0.747 for the catheter in question. The error occurring when using the same correction factor when the body temperature of the animals is different and the length of the intravascular catheter varies, is of a magnitude of 3% (Forrester et al., 1972). The calculation of the area beneath

the curve was carried out by planimetry, using a computer with an optic reader. The method is simple and each determination takes little time, and therefore double determinations do not affect the course of the investigation. Double determinations were carried out of all the measurements of cardiac output in investigations V and VI. The coefficient of variation for these double determinations is in investigation V: 3.6% and in investigation VI: 3.9%. The method of measurement is not affected by the induced changes in pH.

5.2. TOTAL SPLANCHNIC PERFUSION

Total splanchnic perfusion and total liver circulation are equal, providing the anastomoses between the portal and caval circulations are small. The liver blood flow can be measured directly by collection of blood from the hepatic vein, or by the insertion of a "flow-meter" in the afferent vessel to the liver. This technique produces trauma and even the new method using an electromagnetic flow probe around the portal vein and hepatic artery requires extensive surgery.

Clinical investigations have demonstrated that the surgical trauma is the determining factor with regard to the fall in total liver flow during anaesthesia and surgery (Gelman, 1976). The liver blood flow can be measured indirectly, invasively, but almost atraumatically using the clearance technique (Bradley et al., 1945, Caesar et al., 1961, Winkler et al., 1965). The clearance by the liver of the compounds employed is changed by the anaesthesia and this makes the method more difficult to employ during anaesthesia (Price et al., 1966 a).

The liver blood flow can, as other organ flows, also be measured indirectly by means of radioactive isotopes (Kety, 1949).

The pharmacological influence of the anaesthetic agent on the function of liver cells is of no importance in this respect. The method is non-invasive, when the liver flow is measured after the inhalation of radioactive inert gases (Schmitz-Feyerhake et al., 1975), and the portal flow can be measured after the administration of xenon¹³³ into the stomach (Leevy et al., 1973).

These methods are unsuitable for the investigations carried out here (I-VI). The radioactive isotope can be injected retrograde into the hepatic vein with the catheter in the wedge position (Lundbergh & Strandell, 1974) or directly into the liver parenchyma (Lewis et al., 1966). This gives non-uniform administration of the isotope and the possibility of local trauma of the liver parenchyma. Uniform administration of the tracer for several consecutive measurements can best be achieved by injecting the isotope into the portal vein or the hepatic artery (Rees et al., 1964, Darle, 1970, Larson et al., 1973).

If xenon¹³³ is employed, the registration of radioactivity can be carried out externally, and the surgical trauma is therefore limited to the insertion of the catheter into the portal vein or hepatic artery. Lower flow rates are measured following injection into the hepatic artery than after injection into the portal vein (Rees et al., 1964, Larson et al., 1973). The flow which is registered after portal injection of xenon¹³³ and external registration of the radioactivity, is in good agreement with the direct

measurement of total outflow from the hepatic vein (Darle, 1970), and this method has therefore been employed in the present studies.

The external registration of changes in activity in relation to time after the administration of tracer via portal injection has demonstrated a brief ascending part, a top with a more or less pronounced plateau, followed by a down slope (Darle, 1970).

The down slope is related to the blood flow: liver blood flow ($\text{ml g}^{-1} \text{ min}$) = $(\ln 2 \times \lambda) / T_{\frac{1}{2}}$ λ is the partition coefficient which gives the relationship between the concentration of the gas in the tissue and in the blood at equilibrium. $T_{\frac{1}{2}}$ is the half life of the decrement curve.

The relationship of the registered curve to the actual flow is dependent on: 1) the extent to which radioactivity from the neighbouring organs influences the curve. 2) curve calculation, 3) partition coefficient between blood and tissue for the tracer.

Ad.l:if xenon¹³³ is injected into the portal vein via a catheter and the radioactivity measured externally over the liver, there is the possibility that the curve may contain components from the neighbouring organs and residual activity from the catheter. Xenon¹³³ is eliminated almost completely via the lungs, but a few per cent pass the lungs and can, after repeated measurements, accumulate in the stomach/duodenum. In cats, the slow component of the curve represents slow removal of the xenon from the lungs, whereas elimination from the stomach/duodenum is of no importance (Darle, 1970). In contrast, elimination from the lungs appears to

be of no importance during studies in dogs. In these, the extra-hepatic radioactivity comes from accumulation of xenon¹³³ in the stomach and intestines (McKenzie et al., 1976). Such species differences can occur when the size of the organs, their anatomical relation, fat content and blood flow differ. Residual activity in the catheter is probably insignificant (Darle, 1970). In these investigations (I-VI) a detector with a diameter of 4 cm was used. It was placed at the end of a tubular lead collimeter of 10 cm in length. The dogs were placed in the supine position and the free end of the collimeter was in contact with the surface of the animal above the liver.

Ad. 2: Externally registered curves never represent a monoexponential decay. The first part after the top is concave towards the time axis, and the following part is nearly composed of two or more monoexponential decay curves (Darle, 1970, MacKenzie et al., 1976), with a very large difference in the time constant. The calculation can be carried out according to a) "Height over area" principle (Zieler, 1965), b) "resolving into components" (Svein=dottir, 1965), c) "initial-slope" principle.

The first two methods require prolonged registration in order to achieve almost the whole curve (approx. 20 minutes). Darle (1970) used "resolving into components" on externally registered curves following portal injection. He found two components: a very slow one with a half life varying from 3.7 to 30 minutes, and a rapid component with a half life varying from 0.35 to 1.25 minutes. Flow calculation by means of the rapid phase agreed well with the simultaneously registered total outflow from the liver. Within

the flow range studied from 30 to 129 ml 100 g⁻¹ min the flow measurements with portal xenon injection was approximately 10% higher than with directly measured total outflow from the liver. Later Darle & Kock (1971) recalculated the same curves, employing the initial slope principle and found that these values underestimated the total outflow from the liver by approximately 10%. The initial slope principle thus appears to give the same degree of accuracy as resolving into components. The advantage of this method is that the period of registration can be kept short. This is of importance in investigations of this type (I-VI), where changes are made in the dynamics of the circulation and where the total measuring sequence has to be as short as possible.

In investigations I-VI, the curve calculation has been carried out in the same manner each time: 15 seconds after the top of the curve, the reading of the down slope was started and thereafter carried out at intervals of 15 seconds. The values were transferred to semilogarithmic paper, the initial slope was drawn after the visual best fit principle and $T_{\frac{1}{2}}$ read.

Ad. 3: The partition coefficient of xenon¹³³ (λ) for tissue/blood is dependent on temperature, tissue fat content and blood haematocrit. It has been estimated as 0.70 (in vitro) and 0.74 (in vivo) for the liver of dogs (Conn, 1961) and 0.72 (in vivo) in rats and rabbits (Andersen & Ladefoged, 1967). In the latter study it was demonstrated that λ rises with a rising fat content, but the correlation was not significant. Investigations on cats have shown a relationship between the fat content of the liver and the partition coefficient (Darle, 1970). With an average fat content of

4.22 (of wet liver weight) λ was 0.70 (in vitro). The fat content varied considerably from the one animal to the other, range 2.97-7.51%. If a fixed value ($\lambda = 0.74$) is used, the error is between + 15% and - 20%. Comparison of the partition coefficient is carried out after correction for variation in blood haematocrit. Comparison is made with a haematocrit of 50 (hct_{50}). The relationship between the actual λ with an actual haematocrit (hct_x) and λ with hct_{50} is $\lambda \text{hct}_x = (\text{hct}_{50} \times 1.69) / (1.05 + 0.013 \times \text{hct}_x)$ (Andersen & Ladefoged, 1965).

Estimations of the blood flow from clearance values of xenon¹³³ without correction of the partition coefficient of tissue to blood for the haematocrit may induce a random error of about $\pm 10\%$.

The animals served as their own controls in these investigations and a fixed partition coefficient has been employed. An attempt has been made to maintain the body temperature and haematocrit of the animals constant during the investigation. It was assumed that the fat content of the liver would not change during the course of the investigation. The weight of the liver is one of the variables in the calculation of the total liver flow. The liver was weighed immediately after it had been removed at the end of the investigation. The gall bladder and blood which ran out of the organ spontaneously were removed before weighing.

Changes in pH do not influence the flow determinations using the xenon¹³³ method. Darle (1970) found that variations of pH within the range 7.36 to 7.04 gave unchanged good agreement between the calculated flow and the measured total outflow from the liver. The quotient between these two values varied from

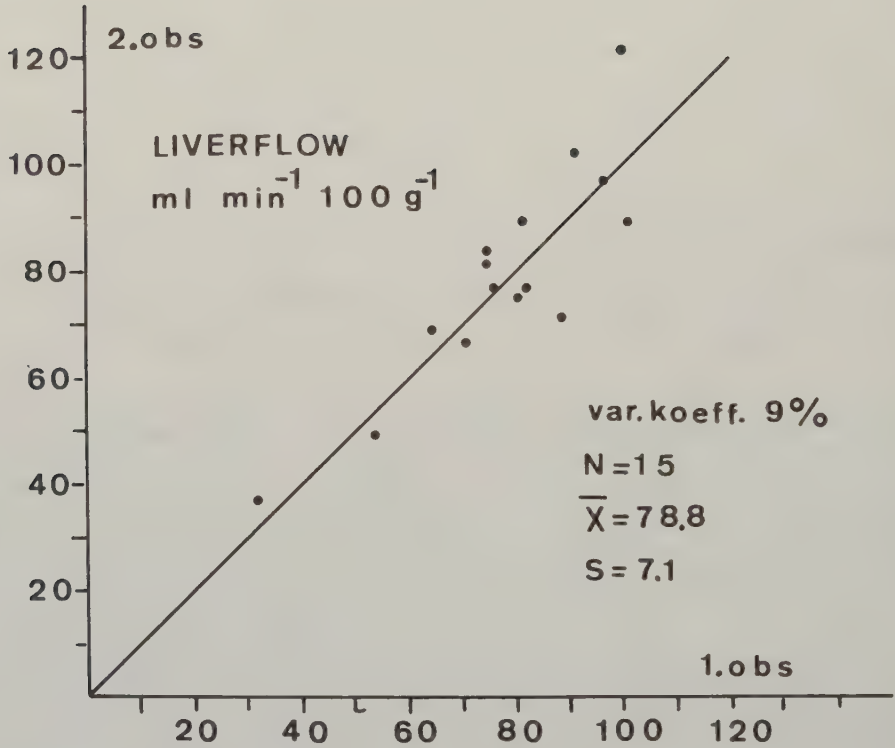


FIGURE 3

DOUBLE DETERMINATIONS OF LIVER FLOW (TOTAL SPLANCHNIC PERFUSION) WITH XENON¹³³ INJECTED INTO THE PORTAL VEIN AND EXTERNAL REGISTRATION OF THE RADIO ACTIVITY

1.14 to 0.98.

The precision of the method has been evaluated on 4 animals, by means of double determinations with the shortest possible time interval (10 - 15 minuter). The second determination was carried out as soon as activity from the first injection had reached a sufficiently low level. The flow per 100 grams of liver tissue can be seen from fig. 3. $N = 15$, range 33 to 122 ml, $\bar{x} = 78.8$ and the coefficient of variation was 9%. This is of the same magnitude as found by Larson et al., (1973), following portal injection in monkeys: 7.4%.

5.3. PRESSURE MEASUREMENTS AND BLOOD SAMPLING

The intravascular pressure measurements were carried out with pressure transducers (Elema-Schönander) positioned with the zero point midway between the sternum and the operating table. The span was adjusted according to the pressure to be measured and the calibration carried out by means of water columns. The pressure curves were registered on a mingograph. In the first investigation (I) the mean pressure was read as the arithmetic mean pressure, but in the subsequent investigations (II-VI) the mean pressure was read after integration of the signal. The heart rate was counted on the ECG registered at the same time (lead II).

Blood samples of 2 ml were withdrawn anaerobically into heparinized glass syringes and immediately tested for pO_2 - pCO_2 and pH. In the first investigations (I-IV) the Astrup apparatus was employed (Radiometer) and in the last two studies (V-VI) an ABC 1

(Radiometer). The measurements were carried out as double determinations. The standard deviation of the double determinations of pO_2 S.D. = 4.8 mm Hg, for pCO_2 the S.D. = 0.9 mm Hg and for pH this S.D. = 0.005. This is the same reproducibility as found by others (Jacobsen, 1977, Ladegaard-Pedersen, 1978). In addition, oxygen saturation was measured in the blood sample (haemoximeter) and the haematocrit determined (capillary method); with regard to the last mentioned measurements, the standard deviation of the double determinations was 0.5%. The oxygen tension and saturation of the blood were only employed in order to ensure that hypoxaemia did not occur during the course of the investigation. The changes in circulation in this survey are compared to the induced changes in arterial pH. No attempt has been made to make any correction for the difference between temperature, pH was measured at (37 degrees C) the body temperature of the animal, but an attempt was made to keep the body temperature of the individual dogs constant.

CHAPTER 6: INTERPRETATION OF MEASUREMENTS

The relationship between the induced changes in acid-base equilibrium and changes in the circulation have been studied using linear regression analysis with the arterial pH as the independent variable, and the respective circulatory variables as the dependent variables. The results of the analysis are shown in the appendix.

pH was chosen as the independent variable because it is the variable which is primarily changed throughout the course of the investigation. The biological activity of hydrogen ions is linearly related to the chemical potential of the hydrogen ions and therefore logarithmically related to hydrogen ion activity and in respect of definition therefore to pH (Ueda & Eyring, 1979). For this reason pH has been chosen and not hydrogen ion concentration.

It is probable that changes in the pH of the cells (pH_i) are determinant with regard to the reactions which are triggered (Price & Helrich, 1955). The contractility of the myocardium (Ng et al., 1967), coronary circulation (Case et al., 1978) and changes in the systemic circulation (Ligou & Nahas, 1960) are thus best related to changes in pH_i . The possibility of using extracellular pH (pH_e) as the independent variable in circulatory investigations will therefore depend on how well pH_e represents pH_i . The best agreement between pH_e and pH_i occurs during carbonic acidosis (Ellis & Thomas, 1976). Non-carbonic acidosis (HCl-infusion) with a pH_e down to 7.0 causes almost no change in pH_i in the myocardium and the striated muscles (Gonzales et al., 1976). pH_e less than 7.0 changes pH_i in an acidic direction with the same strength as with carbonic

acidosis (Adler et al., 1965). It is possible that the relationship between pH_e and pH_i is different in different organs, depending on the buffer capacity of the cells (Clancy & Brown, 1966, Lykkeboe & Johannsen, 1975). It is thus probable that pH_e only approximately represents pH_i . Despite this there are several investigations which have achieved satisfactory interpretation of experimental results using the intravascular acid-base relationship as a reference for circulatory changes.

It is possible that venous blood from different organs has different pH values, whereas pH in the arteries is the same for all organs. In the present investigations arterial pH has been employed as an expression of pH_e and in the following merely written as pH.

A few investigators (Carson et al., 1965, Tomlin et al., 1966) have attempted to formulate equations for cardiac output's dependence on acid-base relationship when the independent variables are the combination of both pH and p_{aCO_2} .

The effect of p_{aCO_2} in these equations, is "pH-adjusted". As mentioned above, it is probable that the changes in pH_i , more than the method by which they are induced are of importance with regard to changes in circulation. Arterial pH has been used as the independent variable both during carbonic and non-carbonic acidosis. It can be seen from the individual investigations whether the changes have primarily been brought about by changes in ventilation (carbonic acidosis) or by the i.v. infusion of hydrochloric acid (non-carbonic acidosis).

The scatter plots of pH and the respective circulatory parametres show a distribution, in some cases, which renders probable a biphasic course of the relationship between the two variables (for example see fig. 2, IV). In several cases the divergence from the linear relationship is, however, so small that it in itself does not give reason to deviate from the law of parsimony (Riggs, 1976) when evaluating the relationship between two variables.

CHAPTER 7: RESULTS

7.1. BASIC ANAESTHESIA

7.1.1. CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION

Progressive carbonic acidosis (IV) brings about a rise in cardiac output during basic anaesthesia. The mean pressure in the aorta and right atrium are not changed, the total peripheral resistance falls and the heart rate remains unchanged.

Similar observations have been made on the same experimental animals during the same type of anaesthesia by Kittle et al., (1965), Andersen og Mouritzen (1966), Manley et al. (1964), Morgan et al. (1967), Wendling et al. (1967) and Carson et al. (1965). These changes in the circulation occur as the combined effect of the central stimulating effect of hypercapnia and peripheral local depressive effects. The increased cardiac output, despite unchanged right atrial pressure, can be accepted as an expression of increased inotropy, but this however, must be seen in the light of the fact that the falling peripheral resistance simultaneously reduces the afterload of the heart.

During light anaesthesia with thiopental and normocapnia changes have been demonstrated in the regional distribution of cardiac output, despite an unchanged arterial pressure. The brain, heart and striated muscles receive an unchanged fraction of the cardiac output, while the kidneys and the intraabdominal organs receive a reduced fraction of the cardiac output (Ahlgren et al., 1978 a). This redistribution, where the flow is best retained to the

organs which react by vasodilatation during hypercapnia, will enhance a fall in the total peripheral resistance.

The effect of carbonic acidosis during basic anaesthesia can also be evaluated by comparing the first observations on the individual animals in investigations II and III. Immediately after the induction of anaesthesia, these animals ($N = 15$) were ventilated in various manners. Some were normoventilated (II) and others mechanically hypo and hyperventilated (III). The individual variation in cardiac output of these animals is partly explained from their differing pH. Cardiac output is greatest in the dogs with hypercapnia. The correlation between pH and cardiac output, however, is insignificant ($0.05 < p < 0.10$).

At the same pH, the cardiac output is higher in the dogs which have had the hypercapnia induced by mechanical hypoventilation (III), than in the dogs which were made hypercapnic during mechanical normoventilation and rebreathing in the dead space of the apparatus (IV). This is in agreement with the results of Morgan et al. (1967). In their investigation of the cardiac output during hypercapnia and varying IPPV, they also found that the rise in cardiac output during hypercapnia was least when the intrathoracic pressure was greatest (IV).

The influence of hypercapnia on heart rate is also afferent by the ventilation. During mechanical normoventilation, the administration of CO_2 brings about no change in heart rate (Andersen & Mouritzen, 1966). Morgan et al. (1967) have shown that carbonic acidosis during mechanical hyperventilation causes a slight but

insignificant rise in heart rate. The unchanged heart rate, which was demonstrated in investigation IV, is in agreement with these results. Thus the sympathetic stimulating effect of hypercapnia does not bring about a rise in heart rate during basic anaesthesia and IPPV. The explanation might be a simultaneous increase in parasympathetic activity. Vagal tone is increased during hypercapnia (Campbell, 1955) and, in addition, the increase in intrathoracic pressure during IPPV stimulates the vagus (Jonzon, 1977). The latter effect is least during hypoventilation and accordingly the type of ventilation interferes with the effect of hypercapnia on heart rate. The relationship between heart rate and pH in investigations II and III is possibly brought about by the concomitant change in ventilation. The correlation is low.

7.1.2. CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION

Progressive hypercapnia (IV) produces a biphasic change in splanchnic perfusion. Firstly the flow increases slightly and thereafter it decreases. The proportion splanchnic perfusion/cardiac output is correlated to pH. This fraction falls from the normal approximately 25% during normocapnia to 15% during hypercapnia at pH 7.1. The vascular resistance is slightly, but insignificantly increased. The pressure in the portal vein rises.

Hughes et al. (1979) have also demonstrated that total splanchnic perfusion in dogs during barbiturate anaesthesia and mechanical normoventilation is changed in a biphasic manner when the animal is exposed to hypercapnia. The two investigations are, however, not immediately comparable because the hypercapnia was brought

about by two different methods. Hughes et al. (1979) observed flow changes within a period of 20 minutes, where CO_2 , in a constant concentration, was added to the inspiratory air. In investigation IV, a slowly progressive hypercapnia was used, which was brought about by rebreathing in the dead space of the apparatus. Changes in the dead space were carried out at intervals of 30 minutes (acclimatization: 15 minutes and sequence measurements 15 minutes). This time interval is insufficient to achieve a steady state for the whole organism, as several hours are required for this (Fahri & Rahn, 1960), but it is sufficient to secure an almost steady arterial pH during measurements. This can be seen from the fact that further 30 minutes of ventilation with the same dead space only produced a maximum change in arterial pH of 0.05 (IV, fig. 1, page 499). Despite the fact that investigation IV and Hughes et al.'s (1979) experimental procedures differed the results can be interpreted in the same manner: the sympathetically mediated vasoconstriction of hypercapnia becomes more and more important during the progression of the hypercapnia (Manley et al., 1964). The slow increase in acidosis as in investigation IV has enhanced this effect.

However, the total vascular resistance in the splanchnic bed did not rise significantly, but this total resistance is only a rough expression of vascular reaction in different parts of the splanchnic area. The pressure in the portal vein, which rises during hypercapnia thus has considerable influence on the preportal resistance in the blood vessels (Mitzner, 1974, b). In the extra-splanchnic systemic circulation, the dominating effect of hypercapnia is vasodilatation and the fraction splanchnic perfusion/

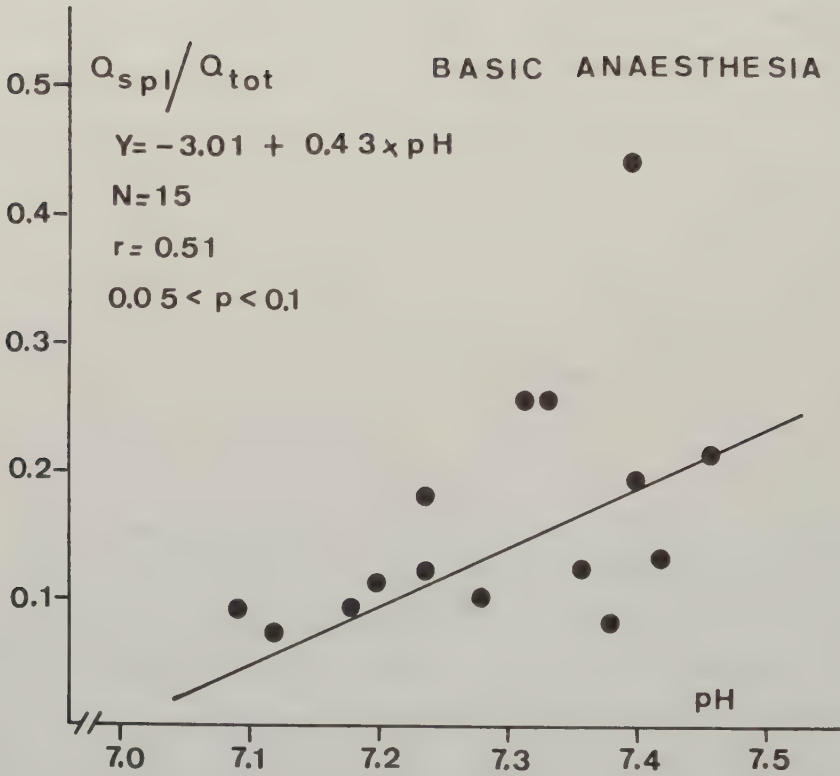


FIGURE 4

CHANGES IN SPLANCHNIC PERFUSION (Q_{SPL}) AS A FRACTION OF CARDIAC OUTPUT (Q_{TOT}) IN RELATION TO ACUTE CARBONIC ACIDOSIS. ONE OBSERVATION ON EACH OF 15 EXPERIMENTAL ANIMALS DURING BASIC ANAESTHESIA (INVESTIGATIONS II + III).

cardiac output is therefore falling.

If changes in p_{aCO_2} are induced by hypo and hyperventilation (initial values in investigation III), the perfusion of the splanchnic bed is least in the hypercapnic dogs. However, in these dogs it is almost of the same magnitude as in normoventilated dogs at the start of investigation II. A scatter plot of the individual figures of Q_{spl}/Q_{tot} and pH from the 15 animals (investigations II + III) is shown in Fig. 4. A relation between Q_{spl}/Q_{tot} and pH appears to be present, but the correlation is insignificant at the 5% level.

7.1.3. NON-CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION

In investigation V the non-carbonic acidosis (pH down to 6.8) was induced by the i.v. infusion of hydrochloric acid. Cardiac output fell to 78% of the initial value. The change is insignificant ($p > 0.05$). There was no correlation between pH and cardiac output. The mean pressure in the right atrium and aorta were unchanged. The peripheral resistance rose by 50% and the heart rate fell.

Changes in the cardiac output are of the same order of magnitude as demonstrated by others (Kittle et al., 1965, Smith & Corbascio, 1966). The rise in plasma catecholamines is related to changes in pH, but independent of whether the acidosis is carbonic or non-carbonic (Morris & Millar, 1962, a, b). The effect of non-carbonic acidosis on the blood vessels is, on the other hand, different from the effect of carbonic acidosis. The infusion of HCl-solution with variations in pH down to 7.0, does not change the vascular

resistance in the coronary vessels (Kittle et al., 1965) or cerebral vessels (Harper & Bell, 1963). Neither does the resistance in the kidneys change (Simmons & Oliver, 1965) nor there is a slight rise (Kittle et al., 1965). The resistance in the blood vessels of the muscles and skin falls slightly (Deal et al., 1954). The vascular resistance in the splanchnic bed rises sharply (V). It is in agreement with these regional changes during non-carbonic acidosis that the total peripheral resistance rises. The same has been demonstrated by Kittle et al., (1965) as well as by Smith & Corbascio (1966). The increasing oxygen extraction, despite unchanged oxygen consumption (V) suggests that the cardiac output is reduced. Reduced inotropy of the myocardium is hardly the explanation. The pressure in the right atrium (V) and in the right ventricle (Smith & Corbascio, 1966) are not changed by non-carbonic acidosis. In vivo the buffer capacity of the heart muscle is large. The intracellular pH of the myocardium is thus unchanged even though the pH of the blood is reduced to 7.08 by means of hydrochloric acid infusion (Gonzalez et al., 1976). The in vitro demonstrated depression of inotropy during acidosis (McElroy et al., 1958) is counteracted in vivo by the sympathetic stimulating effect of the acidosis. As mentioned, the parasympathetic nervous system is also stimulated by acidosis (Cambell, 1955), but it is questionable as to whether increased vagus activity depresses ventricular contractility (Levy, 1976). Changes in sympathetic activity have a very pronounced effect on inotropy. The parasympathetic system, on the other hand, has considerable influence on the electrophysiological conditions in the atrioventricular node and sino-atrial node (Mason, 1968) and the reduction in heart rate (V) suggests that there is a parasympathetic dominance at this site.

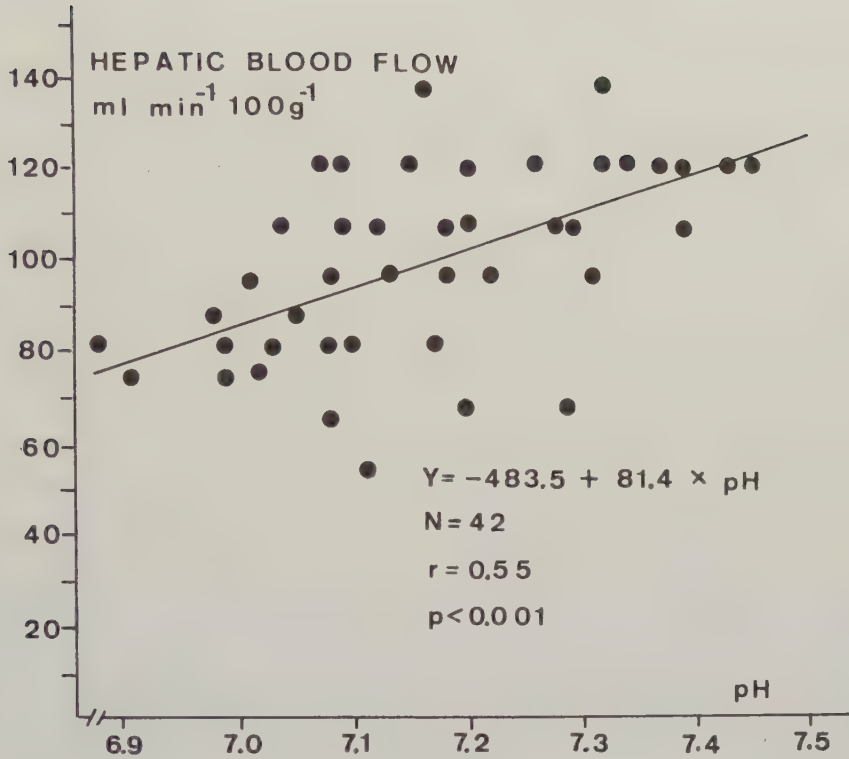


FIGURE 5

CHANGES IN THE LIVER FLOW IN RELATION TO ACUTE NON-CARBONIC ACIDOSIS (I.V. INFUSION OF 0.3 n HCl), THE RESULTS ARE FROM 7 EXPERIMENTAL ANIMALS DURING BASIC ANAESTHESIA (INVESTIGATION V),

7.1.4.

NON-CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION

Non-carbonic acidosis (V) reduced the splanchnic perfusion by 28%. Changes in flow were correlated to pH ($p < 0.001$) (Fig. 5). The vascular resistance in the splanchnic bed rose by 50% and the pressure in the portal vein increased. The fraction splanchnic perfusion/cardiac output (Q_{spl}/Q_{tot}) remained unchanged.

McGinn et al., (1967) have demonstrated in cats that systemic acidosis brought by the i.v. infusion of HCl, does not change the vascular resistance in the vessels of the small intestine, when the perfusion pressure was kept constant. These observations must, however, be seen in the light of the fact that 3 of the 5 experimental animals, before the acidosis was produced, had been investigated under alkalosis (bicarbonate infusion i.v.) and in addition, 3 of the animals were ventilated to an end-tidal CO_2 of 25 mm Hg. The animals were, as in investigation V, anaesthetized with mebumal natrium, but McGinn et al. (1967) induced the anaesthesia by intraperitoneal injection of this compound, which in solution is strongly alkaline. As mentioned (section 2.3) the mesenteric artery and vein do not change their tone when the concentration of hydrogen ions is increased locally (Rogers et al., 1965, Gollwitzer-Meier & Bohn, 1930), whereas the portal vein reacts with increasing resistance and rising pressure to both carbonic and non-carbonic acidosis (Gelman & Ernst, 1977). Non carbonic acidosis thus has little or no vascular dilating effect in the splanchnic bed, which can counteract the sympathetically mediated vasoconstriction. Reduction in the flow of the splanchnic area occurs parallel with a reduction in cardiac output.

7.2. HALOTHANE ANAESTHESIA
7.2.1. CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION

During halothane anaesthesia (IV) carbonic acidosis causes a rise in cardiac output and a fall in the peripheral resistance. The mean pressure in the right atrium and aorta, as well as the heart rate show no variation in relation to the changes in pH.

The haemodynamic effects of the anaesthetic agent are related to the sympatho-adrenergic response they trigger (Price et al., 1959). Halothane does not stimulate the sympathetic system. It has been demonstrated with regard to both man (Price et al., 1959, Stokke et al., 1978) and dogs (Millar & Morris, 1960, Perry et al., 1974) that the concentration of plasma catecholemines is the same during halothane anaesthesia as during anaesthesia with barbiturates. The preganglionic sympathetic activity in the cervical sympathetic trunk and barostatic reflexes are unchanged (Millar & Biscoe, 1965), or very slightly depressed by halothane (Skovsted et al., 1969).

If the sympathetic system is stimulated by carbonic acidosis, the plasma concentration of catecholamines rises (Millar & Morris, 1960), just as much during halothane anaesthesia as during anaesthesia with barbiturates.

The preganglionic sympathetic activity is slightly depressed during halothane anaesthesia (Skovsted et al., 1969), but the increase in this activity during respiratory acidosis is of the same order of magnitude as during basic anaesthesia (Skovsted et al., 1972).

Even though halothane itself does not stimulate the sympathetic system, it apparently does not depress some of the reactions which are triggered by sympathetic stimulation.

It is in agreement with this that the relationship between cardiac index and pH (IV, page 494, Fig. 1) during anaesthesia with 1% halothane lies at a lower level than the corresponding relationship during basic anaesthesia. The slope of the two lines does not differ. Calculated by means of the two correlation equations, the cardiac index is $1.03 \text{ ltr. min}^{-1} \text{ m}^{-2}$ lower during halothane at pH 7.1 and $0.98 \text{ ltr. min}^{-1} \text{ m}^{-2}$ lower at pH 7.4. The last mentioned figure equals a 41% reduction in cardiac index during basic anaesthesia. It is thus of the same order of magnitude as that demonstrated by Ahlgren et al., (1978 b), who found during normocapnia that the cardiac output fell by 43% when the dogs under light barbiturate anaesthesia were subjected to the addition of 1.5% halothane in atmospheric air.

From the very first reports on halothane (Raventos, 1956) to the later published investigations on haemodynamics of this inhalation anaesthetic (Ahlgren et al., 1978 b), it has been demonstrated that the arterial pressure and heart rate decrease during halothane anaesthesia. The reason for this hypotensive effect of halothane is still unsettled. Referring to what has been mentioned on activity in the sympathetic nervous system during halothane anaesthesia, it might be presumed that it mainly results from a peripheral effect of the anaesthetic even though a central effect has also been assumed (Price & Morse, 1963). The fall in blood pressure is dependent on the concentration of halothane (Raven-

tos, 1956). At normal pH (initial values in investigations V & VI), the blood pressure was 29% lower during halothane anaesthesia $\frac{1}{2}$ % in O_2-N_2O than during basic anaesthesia and the heart rate was 23% lower. The corresponding changes during $1\frac{1}{2}$ % halothane in atmospheric air were found to be 25% and 30% respectively after 30 minutes of anaesthesia and 27% and 22% after 120 minutes of anaesthesia (Ahlgren et al., 1978 b).

If carbonic acidosis is induced during halothane anaesthesia (Millar & Morris, 1960), the mean atrial pressure is reduced and the heart rate rises. The reverse sequence, i.e. the addition of halothane during respiratory acidosis (IV) reduces the blood pressure and the heart rate falls. During respiratory acidosis, halothane thus affects the blood pressure and pulse rate in the same direction as that during normocapnia.

During basic anaesthesia, the pulse rate and blood pressure did not correlate to pH (IV) and this was not the case either during halothane anaesthesia (IV).

During normocapnia Ahlgren et al. (1978 b) found insignificant changes in the total peripheral resistance, both after 30 and 120 minutes of halothane. The initial values at normal pH in investigations V and VI are in agreement with this. In addition, halothane does not interfere with the effect of carbonic acidosis on total peripheral resistance. The correlation between the total peripheral resistance and pH during halothane anaesthesia is equal to the corresponding relationship during basic anaesthesia (IV).

7.2.2.

CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION

During halothane anaesthesia, the splanchnic perfusion is higher during hypercapnia than during normocapnia (IV). The difference is not significant. The flow and vascular resistance in the splanchnic bed is not correlated to pH. Splanchnic perfusion as a fraction of cardiac output (Q_{spl}/Q_{tot}) is, during halothane anaesthesia, 0.21 and this does not change within the investigated pH interval. The pressure in the portal vein is higher during carbonic acidosis than during normocapnia.

It is well known, that halothane reduces splanchnic perfusion and this is also confirmed by these investigations (I, IV, V, VI). During normocapnia (initial values in V, VI) the splanchnic perfusion is 38% lower during $\frac{1}{2}\%$ halothane than during basic anaesthesia. In investigation I (the last measurements at normocapnia) the flow is reduced by 45% during 1% halothane. Similar results have been demonstrated by others. In clinical investigations there is a reduction of 30% of the preanaesthetic values during 1.2% - 1.6% halothane (Epstein et al., 1966). Splanchnic perfusion in dogs during light anaesthesia with barbiturates- N_2O-O_2 is reduced 42% - 46%, following the addition of 1% - 2% halothane (Irestedt et al., 1975), and by 43% when $1\frac{1}{2}\%$ halothane in atmospheric air is administered (Ahlgren et al., 1978 b).

During normocapnia, halothane produces an increased resistance in the hepatic artery, whereas the resistance in the preportal area remains unchanged (Ahlgren et al., 1978 b, Irestedt et al., 1978). It is in agreement with this that the total resistance (R_{spl})

during normocapnia in investigations I,V,VI is slightly, even though non-significantly, increased. Similar observations have been made in the previously mentioned clinical investigation of Epstein et al., (1966).

The reduction in splanchnic perfusion during halothane anaesthesia are thus mainly caused by a fall in perfusion pressure.

If hypercapnia is induced during halothane anaesthesia, R_{spl} falls and the splanchnic perfusion rises (Epstein et al., 1966). The present investigations are in agreement with this, even though the sequence of investigation was the reverse: halothane (1%) was added after hypercapnia had been achieved (pH 7.05 - 7.10) during basic anaesthesia. The splanchnic perfusion is thus reduced but only by 15% (IV, fig. 2). although the reduction in cardiac output is twice as large: 30% (IV, fig. 1). Thus cardiac output is redistributed with a relatively greater perfusion of the splanchnic area. The splanchnic bed receives 20.2% of cardiac output during halothane anaesthesia with normocapnia (Ahlgren et al., 1978 b). This is not changed by hypercapnia. In investigation IV the fraction is 0.21. There is no correlation between this fraction and pH within the studied range. In investigation number I, both p_{aCO_2} and the halothane concentration were changed simultaneously but in investigation IV the carbonic acidosis was changed during a fixed concentration of halothane. In the two investigations the relationship between liver flow and cardiac index was not significantly different. During halothane anaesthesia hypercapnia thus produces uniform changes in splanchnic perfusion and in cardiac output. This is in contrast to basic anaesthesia where the

splanchnic area is perfused by falling fractions of a rising cardiac output (IV). The last mentioned reduction in flow is in all probability a sympathetically mediated effect of hypercapnia. The investigations here suggest that this effect is greatly reduced or almost counteracted by halothane. The sympathetic nervous system related to the splanchnic area, appears to be particularly sensitive to the depressive effect of halothane. Haemorrhage with arterial hypotension increase the discharge rate in the splanchnic nerves but this reaction is markedly depressed by halothane (Millar & Briscoe, 1965), and the mesenteric ganglions are more easily blocked by halothane than the cervical ganglions (Raventos, 1956). Investigations IV renders possible that it is a partial block. The elevated portal pressure by hypercapnia remains unchanged after the addition of halothane (fig. 4, IV), despite a reduction in splanchnic perfusion. Only the removal of acidosis normalized this portal pressure.

7.2.3.

NON-CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION

During halothane anaesthesia, non-carbonic acidosis was induced by the intravenous infusion of hydrochloric acid solution (VI). Cardiac output fell to 73% of the initial value. There were no significant changes in the mean pressure of the right atrium and aorta. The peripheral resistance rose to the double. The heart rate remained unchanged down to pH 7.0. At this pH ventricular fibrillation suddenly occurred.

As previously mentioned, halothane does not stimulate the sympathetic nervous system. On the other hand, sympathetically mediated

reactions are only slightly damped by halothane. This is confirmed by the results achieved in investigations V and VI. If the autonomic nervous system is stimulated by non-carbonic acidosis, it produces uniform changes in the systemic circulation during basic and halothane anaesthesia. During the latter anaesthesia, the changes take place at a lower level. The reduction in cardiac output at pH 7.0 is almost of the same order of magnitude, during halothane and basic anaesthesia, 27% and 22% respectively. The relative changes in the peripheral vascular resistance are greatest during halothane anaesthesia, but the most pronounced increase in vascular resistance during this anaesthesia occurs just before the circulation collapses. No relationship could be demonstrated, neither during basic nor during halothane anaesthesia between non-carbonic acidosis and mean pressure in the right atrium and aorta. The most obvious difference in the effect of non-carbonic acidosis on the systemic circulation during the two anaesthesias was seen in the heart rate.

At the start of the investigations (prior to the induction of acidosis) the mean value for the heart rate was 173 min^{-1} during basic anaesthesia (V) and 133 min^{-1} during halothane anaesthesia (VI).

It is well-known that halothane reduces the heart rate during normal acid-base conditions (Raventos, 1956). In clinical anaesthesia this vagus stimulating effect is counteracted by the use of atropine, which was not employed in these investigations.

Non-carbonic acidosis brings about a falling heart rate during

basic anaesthesia (V). The combined effect of halothane (1%) and non-carbonic acidosis (pH 7.0) produces ventricular fibrillation, which is, however, not preceded by any extreme form of bradycardia. It is therefore probable that causes other than extreme imbalance in the autonome nervous system contribute to the arrhythmia on the heart. The most important in this respect is that intracellular acidosis occurs in the heart muscle during non-carbonic acidosis with hydrochloric acid, when extracellular pH comes down to 7.0 (Gonzalez et al., 1976). In addition to this, the cardiac output during halothane anaesthesia is reduced at this pH so much that the oxygen supply to the organism becomes insufficient. The rising arterio-venous oxygen extraction indicates this. Some authors (Boyd et al., 1959, Krauss et al., 1975) have pointed out that the limit between adequate and inadequate cardiac output lies at an oxygen extraction which produces oxygen saturation of mixed venous blood of 60%. This value of oxygen saturation in mixed venous blood occurs immediately prior to the occurrence of ventricular fibrillation (VI).

7.2.4.

NON-CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION

During halothane anaesthesia non-carbonic acidosis brings about a slight rise and thereafter a fall in splanchnic perfusion. The changes are not significant. At pH 7.0 the flow is of the same order of magnitude as with normal pH. As the cardiac output is reduced by non-carbonic acidosis, the fraction splanchnic perfusion/systemic circulation (Q_{spl}/Q_{tot}) increases from 21% at normal pH to 40-50% at pH 7.0. A negative correlation was demonstrated between pH and Q_{spl}/Q_{tot} . The total vascular resistance in the

splanchnic bed is not changed by changes in pH. On the other hand, the pressure in the portal vein and pH are negatively correlated. At pH 7.0 the pressure is twice that of the initial value.

During basic anaesthesia, non-carbonic acidosis causes a reduction in splanchnic perfusion and a rise in splanchnic vascular resistance (V). Compared of this, the effect of non-carbonic acidosis on the splanchnic perfusion during halothane anaesthesia is almost of the type "no-response". This can hardly be explained by the halothane counteracting the stimulating effect of non-carbonic acidosis on the sympathetic nervous system. As mentioned, the peripheral vascular resistance rises, also during halothane anaesthesia, when non-carbonic acidosis is induced. The increase is almost greater than that during basic anaesthesia. It is therefore more probable that it is that part of the sympathetic nervous system which is related to the splanchnic vessels which is particularly sensitive to the depressive effect of halothane (Raventos, 1956, Millar & Briscoe, 1965).

Halothane modified the effect of carbonic acidosis on the splanchnic perfusion in a similar manner (IV). The direct vasodilatatory effect of carbon dioxide dominates during both basic and halothane anaesthesia, but sympathetically mediated vasoconstriction was sufficient to reduce the splanchnic perfusion during basic anaesthesia. This re-distribution of the cardiac output did not occur with halothane, where hypercapnia produced uniform changes in the splanchnic and extra-splanchnic perfusion.

Electrostimulation of the splanchnic nerve causes contraction of the portal vein (Daniel & Prichard , 1951, Deal & Green, 1956, Greenway & Innes, 1980). The increase in the portal pressure during non-carbonic acidosis and halothane anaesthesia can be interpreted as a sign of stimulation of the sympathetic nervous system having, despite everything, some effect on the blood vessels of the splanchnic area during this anaesthesia. It is, however, also possible that it is a locally triggered reaction, independent of the systemic acidosis (Gelman & Ernst, 1977).

It is in general difficult to carry out interpretations as to active/passive changes in the vessels based on measurement of the intravascular pressure and/or flow alone. Neither is the derived expression: $\text{vascular resistance} = \text{pressure difference} / \text{flow}$ unambiguous in this respect (Green et al., 1944). The very complicated arrangement of the vessels in the splanchnic bed, including the double supply of the liver, naturally contributes to the difficulty in interpretation when the portal and hepatic artery flows are not measured separately. It is, however, probable that the increased pressure in the portal vein, which was found in these investigations, is an expression of vasoconstriction. A support for this is that the increased pressure occurs at the same time as non-significant changes were observed in the pressure in the right atrium, the mean arterial pressure and total splanchnic perfusion. Various hepatic sphincters are present (Knisely et al., 1957) which can be the structural basis for the contraction.

7.3. FLUOROMAR ANAESTHESIA

7.3.1. CARBONIC ACIDOSIS - SYSTEMIC CIRCULATION

Carbonic acidosis causes during fluoromar anaesthesia (III), a rise in cardiac output and a fall in peripheral resistance. The mean pressure in the right atrium and in the aorta, on the other hand, are not pH related. The heart rate is highest in the hypercapnic dogs, but the influence of carbonic acidosis on heart rate is uncertain and strongly affected by changes in mechanical ventilation.

Fluoromar has a sympathetic stimulating effect and during clinical anaesthesia with fluoromar there are increases in pulse, cardiac output and plasma concentration of adrenaline and nor-adrenaline (Cullen et al., 1970). In cats the discharge rate in the cervical sympathetic trunk is increased significantly when the inspiratory concentration of fluoromar is 6% or higher (Skovsted & Price, 1970). The sympathetic nervous system of the dog is stimulated to a lesser degree by fluoromar. During normocapnia increasing concentrations of fluoromar bring about a reduction in cardiac output (II). Compared at anaesthetic equipotency, the reduction is not as pronounced as during halothane anaesthesia. The pulse and blood pressure also show a falling tendency, but the strong increase in the peripheral vascular resistance is taken as an expression of a sympathetic stimulation (II). The content of catecholamines in the blood, however, is not increased in dogs anaesthetized by means of fluoromar (Dobkin et al., 1966).

Clinical investigations have shown that carbonic acidosis causes a more pronounced increase in cardiac output during fluoromar anaesthesia than during anaesthesia with halothane (Cullen et al., 1971). Comparison of investigations III and IV shows the same. The potentiation of the circulatory stimulating effect of carbon dioxide can hardly, according to the above, be explained by the sympathetic stimulating effect of fluoromar. In the investigations (II and III) the changes in mechanical ventilation were of importance with regard to the results achieved. The intra-thoracic pressure is less during hypoventilation than under hyperventilation.

The inhibitory influence of positive pressure ventilation on the venous return is therefore less during hypoventilation than during hyperventilation. This effect of ventilation accentuates the effect of changes in pH.

Moderate hyperventilation is necessary in order to obtain normal pH, as dogs have a tendency to develop non-carbonic acidosis during anaesthesia (Danielson et al., 1975, Dobkin et al., 1976). This can also be seen from investigations II (table 2) and III (fig. 6). During the same sequence of anaesthesia (from basic anaesthesia to 6% fluoromar) the animals in investigations II and III (N = 15) were ventilated so differently that their pH was approximately evenly distributed within the range 7.00 - 7.45. The interindividual variation in the cardiac index of these animals at different depths of anaesthesia can be related to their different pH's. The regression lines for the correlation between cardiac index and pH have the same slope with 1½%, 3%

and 6% fluoromar. This would suggest that fluoromar, in these concentrations, does not have any influence on the effect by carbonic acidosis on the cardiac output.

In contrast to the conditions during basic and halothane anaesthesia, where there were only slight changes in the peripheral resistance, the peripheral vascular resistance increases during anaesthesia with fluoromar (II). This effect is not able to eliminate the direct vasodilatation of carbonic acidosis, but it can explain why the inter-individual variations in the peripheral resistance are not significantly related to the pH of the animal ($r = 0.46$, $0.05 < p < 0.10$). A few ($N = 7$) animals' individual reaction to changes in ventilation (III with 6% fluoromar) show a significant positive correlation between pH and the peripheral resistance ($r = 0.54$, $0.01 < p < 0.05$). The mean arterial pressure and heart rate in these animals are, on the other hand, not related to pH. As to the mean arterial pressure, changes in IPPV have little or no influence on mean arterial pressure (Morgan et al., 1966). The heart rate in contrast, is affected by such changes in mechanical ventilation. The slight increase in heart rate which can be seen during carbonic acidosis is not present when the intrathoracic pressure is high (Morgan et al., 1967). During anaesthesia with IPPV, the effect of carbonic acidosis on heart rate is therefore most pronounced when hypercapnia is combined with hypoventilation, as was the case in investigations II and III. In these, a relationship was demonstrated between heart rate and pH, both during basic anaesthesia and increasing concentrations of fluoromar. In contrast, this relationship is not seen during constant moderate hyperventila-

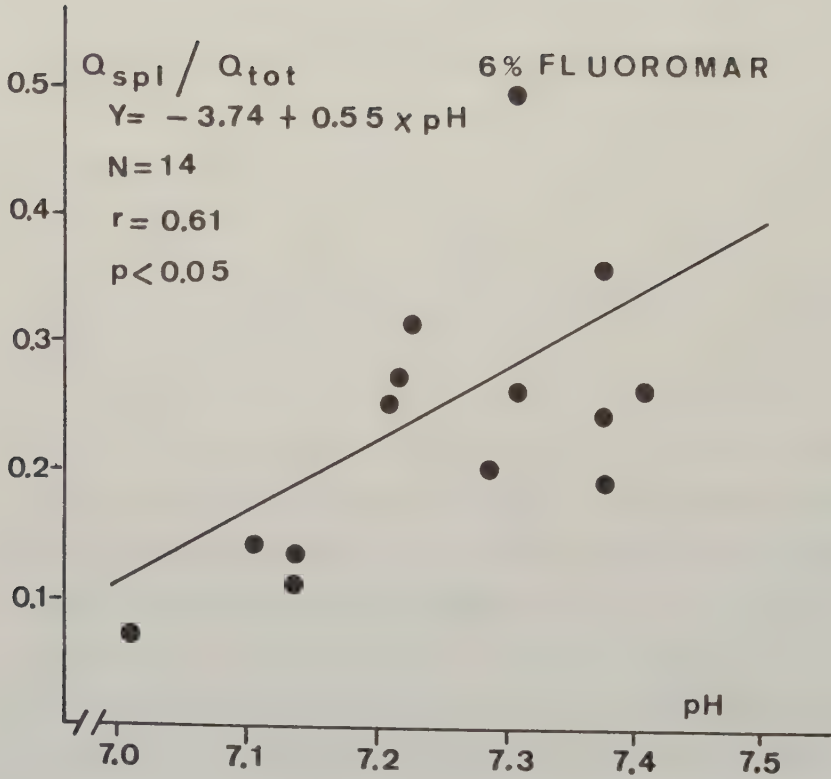


FIGURE 6

THE RELATION BETWEEN SPLANCHNIC PERFUSION (Q_{SPL}) AS A FRACTION OF CARDIAC OUTPUT (Q_{TOT}) AND pH DURING CARBONIC ACIDOSIS AND ANAESTHESIA WITH 6% FLUOROMAR (INVESTIGATION III)

tion with rebreathing (basic and halothane anaesthesia, IV), and when ventilation is suddenly changed (6% fluoromar, III).

Clinical investigations have shown that the rise in pulse rate and blood pressure which carbonic acidosis brings about in non-anaesthetized persons (Sechzer et al., 1960, Cullen & Eger, 1974) is considerably reduced during cyclopropane anaesthesia (Price et al., 1960) and almost counteracted during anaesthesia with halothane (Price et al., 1960, Prys-Roberts et al., 1968). This could suggest that the sympathetic stimulating effect of the anaesthetic agent itself is of decisive importance as to whether hypercapnia during anaesthesia brings about a rise in pulse rate and blood pressure. Other clinical investigations have, however, shown that carbonic acidosis brings about a rise in pulse rate and blood pressure during halothane anaesthesia also (Black et al., 1959, Eikard & Skovsted, 1975). These contrasting results are produced by differences in the depth of anaesthesia, the use of relaxants and spontaneous respiration/mechanical ventilation.

7.3.2. CARBONIC ACIDOSIS - SPLANCHNIC PERFUSION

If carbonic acidosis is induced during fluoromar anaesthesia by changes in the mechanical ventilation, the vascular resistance in the splanchnic bed rises and the perfusion falls. The pressure in the portal vein is highest during hypercapnia, but not significantly. The splanchnic perfusion (Q_{spl}) as a fraction of the cardiac output (Q_{tot}) : Q_{spl}/Q_{tot} goes down with decreasing pH. At the lowest pH ~ 7.0 , it constitutes only 0.1 against 0.25 at normal pH (fig. 6).

As the majority of anaesthetic agents, fluoromar reduces the splanchnic perfusion. The reduction results in all probability from a fall in perfusion pressure as the resistance remains unchanged. Compared to other anaesthetic agents, this reduction is, however, slight (II). At anaesthetic equipotency, it is only half the magnitude of that with halothane anaesthesia. During 6% fluoromar the reduction is 20% which is comparable to the effect on the splanchnic perfusion of neuroleptic anaesthesia (25%) and anaesthesia with barbiturates (15%).

The effect of carbonic acidosis on the splanchnic perfusion during fluoromar anaesthesia (II-III) must also be evaluated in relation to the changes in the mechanical ventilation. During spontaneous respiration the outflow from the splanchnic bed varies with the respiratory cycle. It is greatest during expiration and 180 degrees out of phase with the flow in the inferior caval vein, inasmuch as this is greatest during inspiration (Moreno et al., 1967). IPPV synchronizes these flows, but the mean flow in the splanchnic bed is not changed during normoventilation with normocapnia (Moreno et al., 1967). In contrast, the flow in the splanchnic area is reduced when end-expiratory positive pressure is employed (Johnson & Hedley-Whyte, 1972) and during hyperventilation (tidal volume 40 ml/kg b.w.) with retained normocapnia by the addition of CO₂ (Johnson, 1975). Hyperventilation of the magnitude (14-25 ml/kg b.w.) employed in investigation III must be presumed to have an inhibitory effect on the outflow from the splanchnic bed. Despite this the hypocapnic dogs (pH 7.35 - 7.45) had, however, a higher splanchnic perfusion than the hypercapnic hypoventilated dogs (pH 7.05 - 7.10).

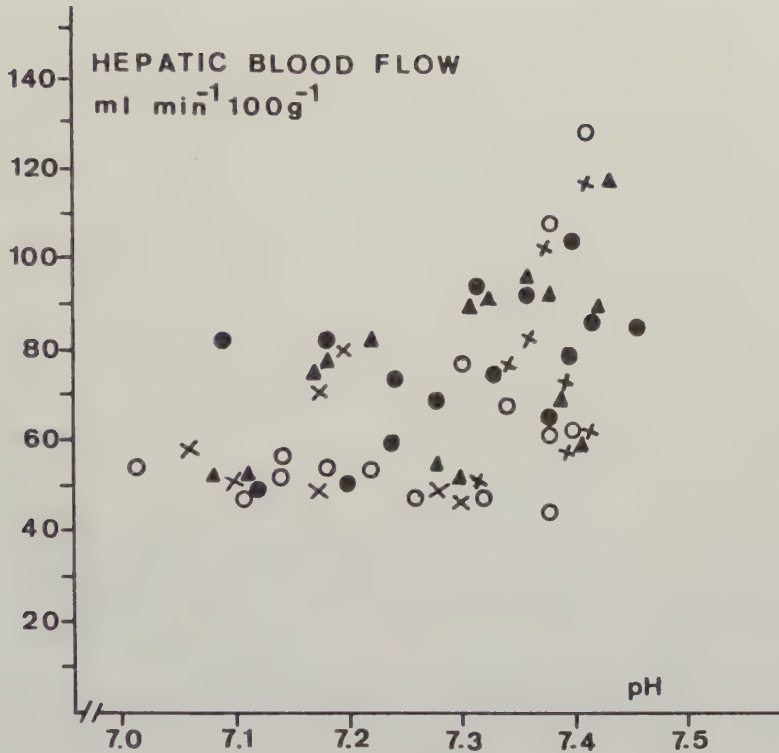


FIGURE 7

CHANGES IN LIVER BLOOD FLOW IN RELATION TO ACUTE CARBONIC ACIDOSIS. THE RESULT FROM 15 ANIMALS FROM INVESTIGATIONS II + III. FOUR MEASUREMENTS HAVE BEEN MADE ON EACH ANIMAL DURING: ● BASIC ANAESTHESIA, ▲ 1½% FLUOROMAR, x 3% FLUOROMAR AND ○ 6% FLUOROMAR, RESPECTIVELY.

A scatter plot (fig. 7) of the liver blood flow of the individual animals ($\text{ml min}^{-1} 100 \text{ g}^{-1}$) and pH during basic anaesthesia (II + III, initial values) shows the same distribution as during basic anaesthesia in investigation IV (fig. 2, page 500), but the correlation is not significant. The scatter in these plots increases with rising concentrations of fluoromar (fig. 7), as fluoromar in itself reduces the splanchnic perfusion. The combined effect of changes in mechanical ventilation and p_{aCO_2} on splanchnic perfusion is, however, still present with 6% fluoromar (fig. 1, page 451 and fig. 5, page 453, III). The alterations in IPPV from hyperventilation to moderate hypoventilation and from hypoventilation to moderate hyperventilation increase liver blood flow. The first mentioned variation brings about this change because of the inhibitory effect of the mechanical ventilation is lessened, without the acidosis being too pronounced and the other variation because the carbonic acidosis is removed without the influence of ventilation on the outflow from the splanchnic bed being too strong.

The relative fraction splanchnic perfusion/cardiac output during basic anaesthesia is related to pH (IV), ($Q_{\text{spl}}/Q_{\text{tot}} = -2.28 + 0.34 \times \text{pH}$, $N = 28$, $r = 0.69$, $p < 0.001$, fig. 3 page 500). The same seems to be the case during basic anaesthesia at the start of investigations II + III (fig. 4, $Q_{\text{spl}}/Q_{\text{tot}} = -3.01 + 0.43 \times \text{pH}$, $N = 15$, $r = 0.51$, $0.05 < p < 0.1$). As can be seen, this correlation is, however, non-significant. The slope of the line (0.43) is strongly influenced by one, in relation to the other measurements, very high value of 0.44. If this measurement is excluded from the calculations, the slope of the line is 0.28,

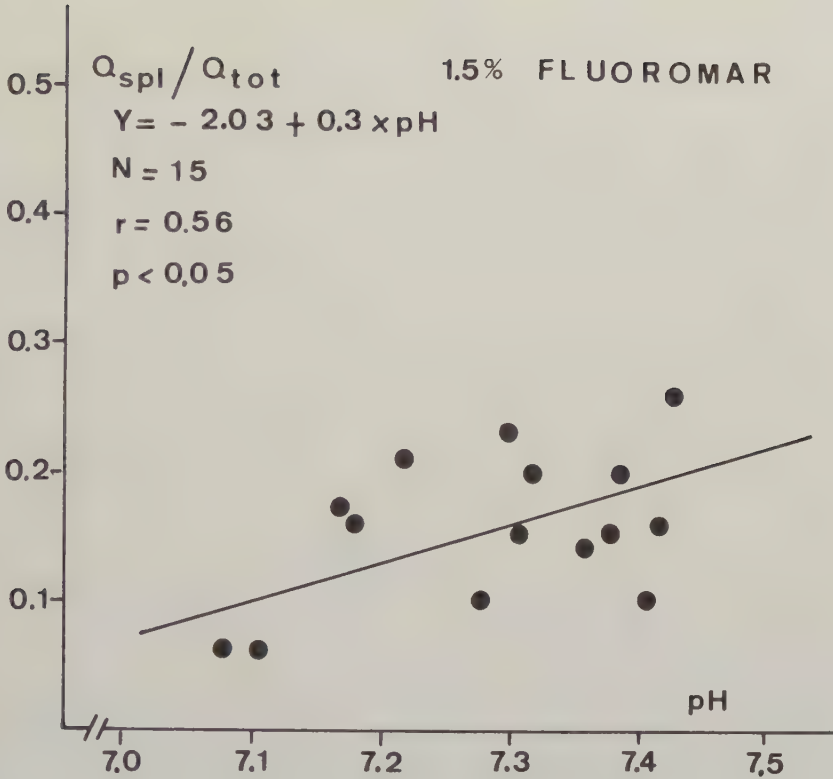


FIGURE 8

CHANGES IN SPLANCHNIC PERFUSION (Q_{SPL}) AS A FRACTION OF THE CARDIAC OUTPUT (Q_{TOT}) IN RELATION TO ACUTE CARBONIC ACIDOSIS, ONE OBSERVATION ON EACH OF 15 ANIMALS DURING 1½% FLUOROMAR (INVESTIGATIONS II + III).

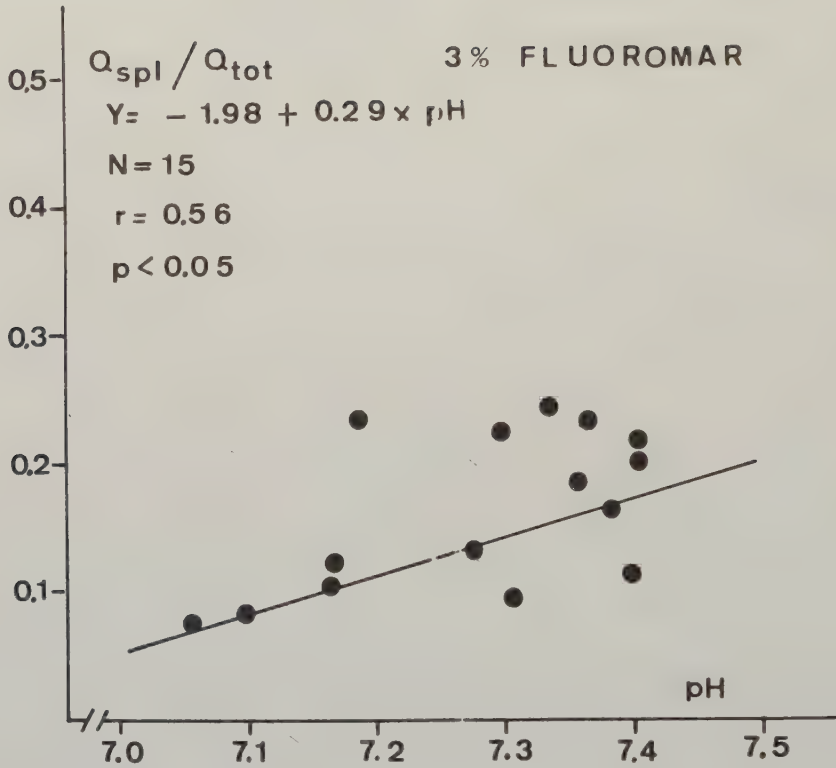


FIGURE 9

CHANGES IN SPLANCHNIC PERFUSION AS A FRACTION OF CARDIAC OUTPUT (Q_{TOT}) IN RELATION TO ACUTE CARBONIC ACIDOSIS, ONE OBSERVATION ON EACH OF 15 ANIMALS DURING 3% FLUOROMAR, (INVESTIGATIONS II + III)

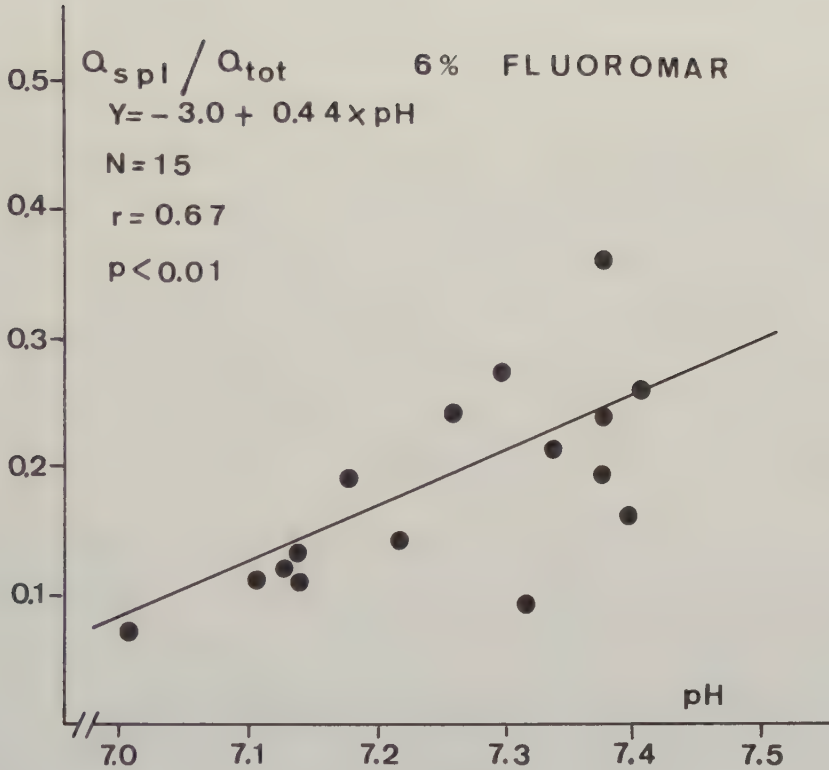


FIGURE 10

CHANGES IN SPLANCHNIC PERFUSION (Q_{SPL}) AS A FRACTION OF THE CARDIAC OUTPUT (Q_{TOT}) IN RELATION TO ACUTE CARBONIC ACIDOSIS. ONE OBSERVATION ON EACH 15 ANIMALS DURING 6% FLUOROMAR (INVESTIGATIONS II + III).

but the correlation is still non-significant ($r = 0.51$, $0.05 < p < 0.1$). Fluoromar in concentrations of 1.5% and 3% does not change the above mentioned relationship between Q_{spl}/Q_{tot} and pH (fig. 8 and fig. 9). The correlations are in fact significant at the 5% level, but as can be seen from the r value: 0.56, there is considerable dispersion. The slope of the lines, 0.30 and 0.29, respectively, are the same as during basic anaesthesia. With 6% fluoromar (fig. 10) the slope is 0.44, significantly ($p < 0.05$) greater than with 3% fluoromar. This can possibly be explained by the sympathetic stimulating effect of fluoromar increasing with exposure time and concentration (Cullen et al., 1970). As mentioned previously, this effect, however, could not be observed on the cardiac output.

During basic anaesthesia and halothane anaesthesia, carbonic and non-carbonic acidosis produce a rise in pressure in the portal vein (IV, V and VI). Carbonic acidosis also appears to increase the pressure in the portal vein during anaesthesia with fluoromar (III, fig. 5, page 453), but the changes are non-significant.

7.4. SUMMARISING THE RESULTS

In agreement with the results of others, it has been found that the arterial blood pressure, heart rate, cardiac output and splanchnic perfusion are highest during basic anaesthesia, less after the addition of fluoromar and least after the addition of halothane. With regard to the two last mentioned anaesthetic agents, the depression of the circulation is, as expected, most pronounced with the highest concentrations.

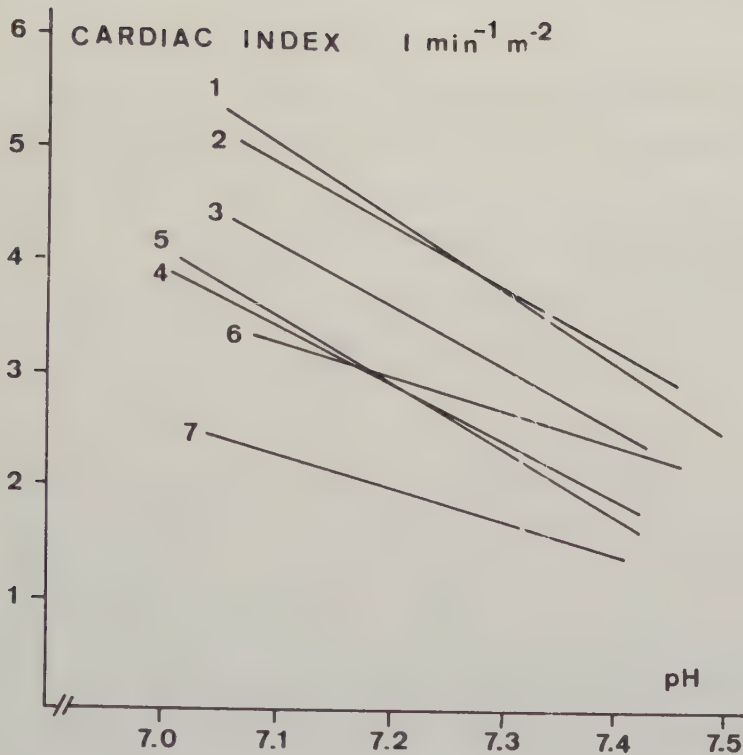


FIGURE 11

REGRESSION LINES FOR CHANGES IN CARDIAC INDEX DURING CARBONIC ACIDOSIS, CURVE 1: BASIC ANAESTHESIA, CURVE 2: 1½% FLUOROMAR, CURVE 3: 3% FLUOROMAR AND CURVE 4: 6% FLUOROMAR, ALL FROM INVESTIGATIONS II + III, CURVE 5: 6% FLUOROMAR WITH A CHANGE IN VENTILATION IN THE MIDDLE OF INVESTIGATION III, CURVE 6: BASIC ANAESTHESIA AND CURVE 7: 1% HALOTHANE FROM INVESTIGATION IV.

The effect of acidosis during the individual anaesthesias is shown schematically in table I. No change could be demonstrated in the mean arterial pressure which could be related to the carbonic or non-carbonic acidosis. The same applies to the pressure in the right atrium.

Carbonic acidosis causes increasing heart rate during basic anaesthesia and anaesthesia with fluoromar, while this is not the case with halothane anaesthesia. Non-carbonic acidosis reduces the heart rate during basic anaesthesia, while during halothane anaesthesia no relationship could be demonstrated between acidosis and heart rate before ventricular fibrillation suddenly occurred at pH 7.0.

Cardiac output rises as a reaction to carbonic acidosis (fig. 11) and falls when non-carbonic acidosis is induced. This is the case during all three forms of anaesthesia. The combination of fluoromar anaesthesia and non-carbonic acidosis has not been studied here, but Stoyka et al., (1970) have demonstrated that the cardiac output and heart rate also fall during this anaesthesia when hydrochloric acid is infused.

The relative changes in cardiac output caused by acidosis are not different during the various anaesthesias, but they take place at various levels, depending on the depressive effect of the anaesthetic agent on the circulation.

In accordance with the above statements on the mean pressure in the right atrium and aorta, the calculated peripheral resi-

stance varies in the opposite direction to the variations in cardiac output.

During basic anaesthesia and fluoromar anaesthesia the splanchnic perfusion is reduced by carbonic acidosis. Non-carbonic acidosis has the same effect during basic anaesthesia. During halothane both forms of acidosis bring about a slight but non-significant rise in splanchnic perfusion.

During all three types of anaesthesia, the pressure in the portal vein rises when carbonic and non-carbonic acidosis are induced.

The adaption of the circulation to acute carbonic and non-carbonic acidosis during anaesthesia and mechanical ventilation are thus mainly changes in flow, caused by changes in peripheral vascular resistance. Both forms of acidosis stimulate the sympathetic nervous system, but the effect of carbonic acidosis on the circulation is dominated by the local vascular dilatating effect of carbon dioxide. The combination of sympathetic stimulation of the heart and a reduction in peripheral resistance bring about a rise in cardiac output. Anaesthesia has little or no influence on this hyperdynamic condition, which, as mentioned, takes place at various levels, depending on the circulatory depressive effect of the anaesthetic agent. In contrast, to what extent the splanchnic perfusion participates in these changes in flow depends on the anaesthesia. During basic anaesthesia the splanchnic perfusion is reduced, when the cardiac output rises during carbonic acidosis. If halothane is added, the splanchnic perfusion and the cardiac output change in a similar manner during carbonic acidosis. This

does not result from a change in reaction due to a greater depth of anaesthesia. If fluoromar is added in equipotent doses, the relationship between splanchnic perfusion and cardiac output are the same as that during basic anaesthesia. A few other investigators have stated that the autonome nervous system associated with the vessels of the splanchnic bed is particularly sensitive to halothane. This can explain the above mentioned observations, and it appears to be confirmed by studies of the circulatory effect of non-carbonic acidosis. The local peripheral effect of non-carbonic acidosis is slight and the over-all effect is a slight fall in cardiac output. This is the case both during basic anaesthesia and after the addition of halothane. The reduction is the same, but takes place at a lower level during halothane anaesthesia, because this anaesthetic is more circulatory depressive than basic anaesthesia. Non-carbonic acidosis, on the other hand, has a different effect on the splanchnic perfusion. During basic anaesthesia the splanchnic perfusion is reduced in line with the fall in cardiac output, during halothane anaesthesia the splanchnic perfusion is unchanged, perhaps even slightly rising while the cardiac output falls.

The flow in the portal vein was not measured separately, and the rise in pressure in the portal vein cannot therefore be evaluated in relation to this. The portal pressure rises during both carbonic and non-carbonic acidosis. This is seen at the same time as the total flow remains unchanged or falls, and without the mean pressure in the right atrium and aorta being changed. The pressure rise is in all probability a real expression of an increased resistance in the post-portal area of the liver. Stimu-

lation of the splanchnic nerve brings about a rise in the portal pressure and as acidosis stimulates the sympathetic nervous system, this can be the explanation of the increased pressure in the portal vein. If so, one would expect that this reaction was more difficult to observe during halothane anaesthesia than during anaesthesia with fluoromar, which is not the case. This would indicate that locally triggered reactions, as stated by Gelman & Ernst (1977) are of importance with regard to the pressure rise in the portal vein as brought about by acidosis.

7.5. CLINICAL ASPECTS

The clinical aspect of a reduced splanchnic perfusion during anaesthesia could be that the individual organs, particularly the liver, were exposed to hypoxia (Price et al., 1966). However, definite indications of this have not been forthcoming. The oxygen consumption of the splanchnic area is reduced during anaesthesia, even though not as much as the reduction in flow. The relative hypoperfusion can be quantitated by relating the oxygen consumption/blood flow during anaesthesia to the corresponding relation pre-anaesthetically. Anaesthetic agents can be ranked using this criterion (Libonati et al., 1973). In this respect, the most favourable (with least flow reduction in relation to oxygen consumption) is halothane, and the least favourable methoxyflurane. It has been demonstrated angiographically that the last mentioned anaesthetic brings about a vasoconstriction of the hepatic artery (Libonati et al., 1973) and increased resistance in the hepatic artery has also been demonstrated during halothane anaesthesia (Frestedt, 1978). Under normal conditions the hepatic artery

supplies 70% of the total hepatic oxygen uptake (Greenway & Stark, 1971), and a reduction in the arterial flow can therefore be considered to be particularly unfavourable.

The oxygen extraction capacity of the liver is, however, very great during reduced flow and under these conditions oxygen extraction of up to 97% - 98% has been measured. Oxygen uptake is independent of the relative flow distribution between the portal vein and hepatic artery (Bauereisen & Lutz, 1975) and the haemodynamic conditions in the liver can be manipulated considerably, without this causing changes in functional capacity (Jacobsen et al., 1969, Tashkin et al., 1972, Krarup, 1976).

It has not been possible to demonstrate a relationship between the normally occurring peroperative reduction in liver flow and the postoperative changes in liver function. On the other hand, the number of patients with postoperatively affected liver function increases when acidosis occurs during anaesthesia. This has been demonstrated clinically with regard to ether and chloroform (Sims et al., 1951) and halothane (Morris & Feldman, 1963). In animal experiments the hepatic cellular lesions after chloroform increase if acidosis occurs during anaesthesia (Galindo et al., 1965).

Studies on animals have shown that changes in the splanchnic circulation influence both preload and afterload, and therefore the cardiac output (Greenway & Innes, 1980). The preload of the heart increases when the capacitance of the splanchnic circulation is reduced. This can occur "actively" by an increase in venous

tone, or "passively" by a reduction in the trans-mural pressure in the veins, when the arterioles contract (Öberg, 1967). Similar observations have been made clinically. The preload of the heart is reduced following the administration of morphine, among other reasons because this drug increases the capacitance and flow in the splanchnic vascular system (Leaman et al., 1978). The blood volume can be reduced by 15% - 20% without the cardiac output and the arterial pressure falling, because the splanchnic blood volume is reduced as a reaction to blood loss (Price et al., 1966). This reduction can take place without the splanchnic vascular resistance increasing. On the other hand, the resistance rises and the flow falls in the splanchnic bed at the same time as the splanchnic blood volume is reduced when the cardiac output rises during muscular exertion (Wade et al., 1956, Clausen & Trap-Jensen, 1974). It has been shown in animal experiments that the amount of blood which can be "passively" mobilized from the splanchnic circulation during sympathetic activation is positively linearly related to the splanchnic blood flow prior to activation (Brooksby & Donald, 1972). To what extent the splanchnic circulation during anaesthesia can be incorporated into the adaptation by the circulation to a circulatory stress, as for example, acidosis, is therefore dependent on the extent to which the splanchnic perfusion has previously been reduced by the anaesthesia. It is possible that this is also the case in man. The splanchnic circulation in man and dogs have many points in common (Greenway & Stark, 1971). The changes in splanchnic perfusion brought about by anaesthetic agents are uniform in the two species, and the same applies to the changes which occur when carbonic acidosis is brought about during anaesthesia with barbiturates

and halothane. In contrast, there is a large species difference in the way in which the splanchnic perfusion reacts when the circulation is exposed to excessive stress, such as haemorrhagic or septic shock (Marston, 1974). Whether these differences also apply when the circulation is so strongly affected as is the case during non-carbonic acidosis and halothane anaesthesia is uncertain. No clinical observations are available which show that the splanchnic area in man is strongly hyperperfused with this combination of acidosis and anaesthesia. In non-anaesthetized man, non-carbonic acidosis in all probability causes a contraction of the splanchnic vessels (Ng et al., 1977). The same reaction is seen in dogs during light barbiturate anaesthesia, an anaesthesia which only interferes slightly with the autonome nervous system. It would appear superficially, rational that the splanchnic perfusion is reduced as a reaction to stress when the other parts of the circulation are stabilized by this. Pronounced hypoperfusion of the splanchnic area is, however, related to the release from the pancreas of myocardial depressive factor (Lefer, 1970), which in the long run can cause circulatory failure.

There are only a few clinical investigations regarding the influence of anaesthesia on the pressure in the portal vein (Varadhan & Silva, 1972, Burcharth et al., 1979). The first mentioned investigation showed that both patients with and without livercirrhosis had lower pressure in the portal vein during laparotomy than either pre- or postoperatively. This was attributed to the influence of the anaesthesia on the perfusion of the splanchnic area, but it is probable that the laparotomy has had an important influence on the results. In the latter investigation, which was carried out

on patients suffering from liver cirrhosis and portal hypertension, there was thus no significant difference between portal pressure measured during anaesthesia and that postanaesthetically. The pressure in this investigation was measured after percutaneous transhepatic puncture, and the measurements were carried out during anaesthesia with thiopental- $\text{N}_2\text{O}-\text{O}_2$ -pancuronium bromide and after the addition of 1% halothane. Provided acidosis has the same effect during clinical anaesthesia as has been demonstrated in animal experiments, it is important to check the acid-base status when the portal pressure is measured during anaesthesia.

SUMMARY

The object of the investigation has been to study the part played by the splanchnic perfusion in the changes which occur in the systemic circulation as a reaction to acute acidosis during anaesthesia, and in particular the influence of the anaesthesia on the reaction thus triggered.

The experimental basis is six investigations carried out on dogs. The results of these were published in *Acta anaesth. scand.* during the years 1974 to 1979.

The induction of anaesthesia was carried out by means of i.v. injection of mebumal natrium (NFN) and after gallamoni judidum the animals were intubated tracheally and artificially ventilated with O_2/N_2O . This anaesthesia was termed basic anaesthesia and in the individual investigations was either continued by refractory doses of mebumal natrium or either halothane or fluoromar were added to the inspiratory air.

Carbonic acidosis was brought about by alveolar hypoventilation, either by changes in the setting of the respirator or by the insertion of increasing dead space between the animal and respirator. Non-carbonic acidosis was induced using i.v. infusion of 0.3 n hydrochloric acid. pH changes were from 7.45 to 6.90.

Cardiac output was measured using the dye-dilution or thermodilution methods and total splanchnic perfusion was measured as total liver perfusion by means of xenon¹³³ injected into the portal

vein and external registration of the activity over the liver.

During normal acid-base condition it was demonstrated in agreement with others, that the arterial blood pressure, heart rate, cardiac output and splanchnic perfusion were highest under basic anaesthesia, less after the addition of fluoromar and least after halothane. With regard to the latter two agents, the depression of the circulation was, as expected, most pronounced with the highest concentrations.

During the individual anaesthesias no changes were demonstrated in the mean arterial pressure, which could be related to the induced carbonic and non-carbonic acidosis. The same applied to the pressure in the right atrium.

During basic anaesthesia and anaesthesia with fluoromar, carbonic acidosis brought about a rising heart rate. Non-carbonic acidosis reduces heart rate during basic anaesthesia and others have demonstrated that this is also the case during anaesthesia with fluoromar. During halothane anaesthesia, no relationship could be demonstrated between carbonic acidosis and heart rate. Non-carbonic acidosis initially caused no change in the heart rate during halothane anesthesia, but at pH 7.0 ventricular fibrillation suddenly occurred.

Cardiac output rises as a reaction to carbonic acidosis and falls when non-carbonic acidosis is induced. This is the case under all three forms of anaesthesia. A combination of fluoromar anaesthesia and non-carbonic acidosis has not been studied here, but Stoyka et

al., (1970) have demonstrated that cardiac output also falls during this anaesthesia, when hydrochloric acid is infused.

The relative changes in cardiac output which are caused by acidosis do not differ under the various anaesthesias, but occur at different levels, depending on the extent of depression of the circulation by the anaesthetic agent.

In respect of the above mentioned mean pressure in the right atrium and aorta, the calculated peripheral resistance varies in the opposite direction to the variation in cardiac output.

During basic anaesthesia and fluoromar anaesthesia the splanchnic perfusion is reduced by carbonic acidosis. Non-carbonic acidosis has the same effect during basic anaesthesia. On the other hand, during halothane anaesthesia both forms of acidosis cause slight non-significant rises in splanchnic perfusion.

During all three anaesthesias the pressure in the portal vein rises when carbonic and non-carbonic acidosis are induced.

The adaption of the circulation to acute carbonic and non-carbonic acidosis during anaesthesia and mechanical ventilation are thus by far changes in flow brought about by changes in the peripheral resistance. Both forms of acidosis stimulate the sympathetic nervous system, but the circulatory effect of carbonic acidosis is dominated by the local vascular dilatating effect of carbon dioxide. A combination of sympathetic stimulation of the heart and reduction of the peripheral resistance brings

about a rise in cardiac output. Anaesthesia has little or no influence on this hyperdynamic condition, which as mentioned occurs at various levels, depending on the circulatory depressive effect of the anaesthetic agent. On the other hand, to what extent splanchnic perfusion plays a part in these flow changes is dependent on the anaesthesia. During basic anaesthesia the splanchnic perfusion is reduced when the cardiac output rises during carbonic acidosis. If halothane is added the splanchnic perfusion and cardiac output change in the same manner during carbonic acidosis. This does not result from a changed reaction due to a deeper anaesthesia. If fluoromar is added in equipotent doses, the relation between splanchnic perfusion and cardiac output is the same as during basic anaesthesia. A few other investigators have stated that the autonome nervous system of the vessels of the splanchnic area are particularly sensitive to halothane. This can explain the above mentioned observations and it appears to be confirmed by investigations of the circulatory effect of non-carbonic acidosis. The local peripheral effect of non-carbonic acidosis is slight and the over-all effect is a slight fall in cardiac outout. This applies to both basic anaesthesia and after the addition of halothane. The reduction is the same, but takes place at a lower level during halothane anaesthesia, because this agent has a greater circulatory depressive effect than basic anaesthesia. On the other hand, non-carbonic acidosis has two entirely different effects on the splanchnic perfusion during the two anaesthesias. During basic anaesthesia the splanchnic perfusion is reduced in step with the falling cardiac output, during halothane anaesthesia the splanchnic perfusion remains unchanged, or may

even be slightly increased at the same time as the cardiac output falls.

The flow in the portal vein has not been measured separately, and the increase in portal pressure cannot therefore be evaluated in relation to this. The portal pressure rises during both forms of acidosis, and this is seen at the same time as the total flow remains unchanged or falls and without the mean pressure in the right atrium or aorta changing. The rise in pressure is in all probability a real expression of an increased resistance in the postportal area of the liver. Stimulation of the splanchnic nerve brings about a rise in portal pressure and as acidosis stimulates the sympathetic nervous system, this can be the explanation of the increased pressure in the portal vein. If so, one would expect that this would be more difficult to observe during halothane anaesthesia than during anaesthesia with fluoromar, which is not the case. This could indicate that locally triggered reactions, as stated by Gelman & Ernst (1977) are of importance with regard to the pressure rise in the portal vein as induced by acidosis.

The possible clinical aspects of the results achieved are discussed.

SUMMARY

Formålet med arbejdet har været at undersøge splanchnicusperfusionens andel i de ændringer, der finder sted i systemkredsløbet som reaktion på akut acidose under anæstesi, herunder specielt anæstesiens indflydelse på de udløste reaktioner.

Det eksperimentelle grundlag er 6 undersøgelser udført på hunde. Resultaterne heraf er offentliggjorte i Acta anaesth. scand. i årene 1974 til 1979.

Anæstesiinductionen er hver gang foretaget med i.v. injection af mebumal natrium (NFN) og efter gallamoni jodidum blev dyrene tracheal intuberede og kunstigt ventilerede med O_2/N_2O . Denne anæstesi, kaldet basisanæstesi, er i de enkelte undersøgelser enten blevet fortsat med refrakte doser af mebumal natrium eller, der er tilsat enten halothane eller fluoromar til inspirationsluften.

Karbonisk acidose blev fremkaldt ved alveolær hypoventilation, enten ved at ændre på respiratorindstillingen eller ved at indskyde tiltagende dead space mellem dyret og respiratoren. Non-karbonisk acidose blev induceret med i.v. infusion af 0.3 normal saltsyre. pH variationerne var fra 7.45 til 6.90.

Cardiac output blev målt med dye-dilution eller thermo-dilution, og total splanchnicusperfusionen er målt som total leverperfusion ved hjælp af xenon¹³³ injiceret i vena portae og extern registrering af aktiviteten over leveren.

Under normale syre-base-forhold blev der i overensstemmelse med andres resultater påvist, at det arterielle blodtryk, hjertefrekvensen, cardiac output og splanchnicusperfusionen var højest under basisanæstesi, mindre efter tilsætning af fluoromar og mindst efter tilsætning af halothane. For de to sidstnævnte stoffers vedkommende, var kredsløbsdepressionen som forventet mest udtalt ved de højeste koncentrationer.

Under de enkelte anæstesier påvises der ingen ændringer i det arterielle middeltryk, der kan relateres til den inducerede karboniske og non-karboniske acidose. Det samme gælder for trykket i højre atrium.

Under basisanæstesi og anæstesi med fluoromar, fremkalder karbonisk acidose stigende hjertefrekvens. Non-karbonisk acidose reducerer hjertefrekvensen under basisanæstesi, og andre har påvist, at dette også er tilfældet under anæstesi med fluoromar. Under halothane anæstesi påvises der ingen sammenhæng mellem den karboniske acidose og hjertefrekvensen. Non-karbonisk acidose fremkalder primært ingen ændring i hjertefrekvensen under halothane anæstesi, men ved pH 7.0 opstår der pludselig ventrikelflimmer.

Cardiac output stiger som reaktion på karbonisk acidose og falder, når non-karbonisk acidose induceres. Dette er tilfældet under alle tre anæstesiformer. Kombinationen af fluoromaranæstesi og non-karbonisk acidose er ikke undersøgt her, men Stoyka et al., (1970) har vist, at cardiac output også falder under denne anæstesi, når saltsyre infunderes.

De relative ændringer i cardiac output, som acidose fremkalder, er ikke forskellige under de forskellige anæstesier, men de foregår på forskellige niveauer, afhængig af anæstesimidlets depression af kredsløbet.

Jævnfør det ovenfor nævnte om middeltrykket i højre atrium og aorta, varierer den beregnede perifere modstand modsat variationerne i cardiac output.

Under basisanæstesi og fluoromaranæstesi reduceres splanchnicusperfusionen af karbonisk acidose. Non-karbonisk acidose har samme virkning under basisanæstesi. Under halothaneanæstesi fremkalder begge former for acidose derimod lette ikke signifikante stigninger i splanchnicusperfusionen.

Under alle tre anæstesier stiger trykket i vena portae, når karbonisk og non-karbonisk acidose induceres.

Kredsløbets adaptering til akut karbonisk og non-karbonisk acidose under anæstesi og mekanisk ventilation er således langt overvejende flowændringer fremkaldt af ændringer i den perifere modstand. Begge former for acidose stimulerer det sympatiske nervesystem, men den karboniske acidoses kredsløbseffekt domineres af kuldioxidens lokale kardilaterende virkning. Kombinationen af sympathicusstimulering af cor og reduktion af den perifere modstand fremkalder stigning i cardiac output. Anæstesen har lille eller ingen indflydelse på denne hyperdynamiske tilstand, der som nævnt udspilles på forskellige niveauer, afhængig af anæstesimidlets kredsløbsdepression. Hvorledes splanchni-

cusperfusionen deltager i disse flowændringer er derimod afhængig af anæstesi. Under basisanæstesi reduceres splanchnicusperfusionen, når cardiac output stiger under karbonisk acidose. Tilsættes halothane, ændrer splanchnicusperfusionen og cardiac output sig på samme måde under karbonisk acidose. Dette skyldes ikke en ændret reaktion på grund af dybere anæstesi. Tilsættes fluoromarkering i equipotente doser, er relationen mellem splanchnicusperfusionen og cardiac output den samme under basisanæstesi. Enkelte andre undersøgere har anført, at det autonome nervesystem med tilknytning til karrene i splanchnicus er særlig følsomme for halothane. Dette kan forklare ovennævnte iagttagelser, og det synes bekræftet af undersøgelserne over non-karbonisk acidoses kredsløbseffekt. Den perifere lokale effekt af non-karbonisk acidose er lille og all-over effekten er et let fald i cardiac output. Dette er tilfældet både under basisanæstesi og efter tilsætning af halothane. Reduktionen er den samme, men den foregår på et lavere niveau under halothaneanæstesi, fordi dette stof er mere kredsløbsdeprimerende end basisanæstesi. Non-karbonisk acidose påvirker derimod splanchnicusperfusionen forskellig under de to anæstesier. Under basisanæstesi reduceres splanchnicusperfusionen i takt med faldet i cardiac output, under halothaneanæstesi er splanchnicusperfusionen uændret, måske endda let stigende samtidig med at cardiac output falder.

Flowet i vena portae er ikke målt separat, og trykstigningen i vena portae kan derfor ikke bedømmes i relation hertil. Portaltrykket stiger under begge former for acidose, og det ses samtidig med, at totalflowet er uændret eller faldende, og uden at middeltrykket i højre atrium og aorta har ændret sig. Trykstig-

ningen er sandsynligvis et reelt udtryk for øget modstand i leverens postportale kargebet. Stimulering af sympatheticus (nervi splanchnici) fremkalder stigning i portaltrykket, og da acidose stimulerer sympatheticus, kan dette være forklaringen på den fundne trykstigning i vena portae, i så fald ville man nok forvente, at trykstigningen var vanskeligere at iagttage under halothane-anæstesi end under anæstesi med fluoromar, hvilket ikke er tilfældet. Dette kunne tyde på, at lokalt udløste reaktioner som anført (Gelman & Ernst, 1977) er af betydning for den trykstigning i vena portae, som acidosen fremkalder.

De mulige kliniske aspekter af de opnåede resultater diskuteres.

APPENDIX

THE RESULTS OF INVESTIGATIONS I-VI ARE COMBINED IN A SINGLE
DIAGRAM: TABLE 1

TABLES 2 TO 6: CIRCULATORY VARIABLES AS A FUNCTION OF PH,

THE REGRESSION EQUATIONS ARE GIVEN WHEN THE COEFFICIENT OF
CORRELATION IS SIGNIFICANT AND $P < 0.05$

		Systemic circulation						Splanchnic perfusion				
Anaesthesia	Acidosis	$\bar{P}_{\text{right atr.}}$	$\bar{P}_{\text{aorta}}$	heart frequ.	O_{tot}	R_{tot}	Q_{spl}	$Q_{\text{spl}}/Q_{\text{tot}}$	R_{spl}	$\bar{P}_{\text{porta}}$		
Basic	carbonic	o	o	(+)	+	-	-	-	o	+		
	non-carbo- nic	o	o	-	-	+	-	o	+	+		
Halothane	carbonic	o	o	o	+	-	(+)	o	o	+		
	non-carbo- nic	o	o	o !	-	+	(+)	+	o	+		
Fluoromar	carbonic	o	o	(+)	+	-	-	-	+	(+)		

The diagram shows in which direction the individual circulatory parameters change as a reaction to acidosis during anaesthesia.

+ = rise, o = no change, - = fall. Note o ! = no change before at pH 7.0 ventricular fibrillation occurred.

Table 1.

CARDIAC INDEX (1 min $^{-1}m^{-2}$) AS A FUNCTION OF pH

ANAESTHESIA	ACIDOSIS	REF. No.	REGRESSION EQUATION	N	r	p
basic	carbonic	IV	$Y = 24.31 - 2.96 \times \text{pH}$	28	-0.47	0.01
halothane 1%	carbonic	IV	$Y = 22.50 - 2.85 \times \text{pH}$	26	-0.45	0.01
fluoromar 6%	carbonic	III	$Y = 45.20 - 5.87 \times \text{pH}$	14	-0.73	0.001
basic	non-carbonic	V	-----	42	-----	n.s.
halothane 1%	non-carbonic	VI	$Y = 21.49 + 3.21 \times \text{pH}$	23	0.75	p < 0.001
basic	carbonic	II+III	-----	15	-----	n.s.
fluoromar 1½%	carbonic	II+III	$Y = 44.60 - 5.60 \times \text{pH}$	15	-0.53	0.01
fluoromar 3%	carbonic	II+III	$Y = 41.83 - 5.31 \times \text{pH}$	15	-0.62	0.01
fluoromar 6%	carbonic	II+III	$Y = 40.13 - 5.17 \times \text{pH}$	15	-0.70	0.001

Table 2.

TOTAL PERIPHERAL RESISTANCE (kPa l⁻¹ min) AS A FUNCTION OF pH

ANAESTHESIA	ACIDOSIS	REF. No.	REGRESSION EQUATION	N	r	P
basic halothane 1% fluoromar 6%	carbonic	IV	$Y = -119 + 17.8 \times \text{pH}$	28	0.53	0.01 < p < 0.05
	carbonic	IV	$Y = -109 + 16.4 \times \text{pH}$	26	0.61	p < 0.001
	carbonic	III	$Y = -81 + 12.6 \times \text{pH}$	14	0.54	0.01 < p < 0.05
basic halothane 1%	non-carbonic	V	-----	42	----	n.s.
	non-carbonic	VI	$Y = 118 - 15.1 \times \text{pH}$	28	-0.45	0.01 < p < 0.05
basic fluoromar 1% fluoromar 3% fluoromar 6%	carbonic	II+III	$Y = -110 + 16.1 \times \text{pH}$	15	0.60	0.01 < p < 0.05
	carbonic	II+III	-----	15	----	n.s.
	carbonic	II+III	-----	15	----	n.s.
	carbonic	II+III	-----	15	----	n.s.

Table 3

HEART RATE (min^{-1}) AS A FUNCTION OF pH

ANAESTHESIA	ACIDOSIS	REF. No.	REGRESSION EQUATION	N	r	p
basic	carbonic	IV	-----	28	--	n.s.
halothane 1%	carbonic	IV	-----	26	--	n.s.
fluoromar 6%	carbonic	III	-----	14	--	n.s.
basic	non-carbonic	V	Y = -396 + 77.8 x pH	42	0.46	0.001 < p < 0.01
halothane 1%	non-carbonic	VI	-----	28	--	n.s.
basic	carbonic	II+III	Y = 1066 - 124.2 x pH	15	-0.68	0.001 < p < 0.01
fluoromar 1%	carbonic	II+III	Y = 1067 - 124.9 x pH	15	-0.68	0.001 < p < 0.01
fluoromar 3%	carbonic	II+III	Y = 1018 - 119.6 x pH	15	-0.66	0.001 < p < 0.01
fluoromar 6%	carbonic	II+III	Y = 837 - 95.4 x pH	15	-0.62	0.01 < p < 0.05

Table 4.

Q_{spl}/Q_{tot} (SPLANCHNIC PERFUSION AS A FRACTION OF CARDIAC OUTPUT) AS A FUNCTION OF pH

ANAESTHESIA	ACIDOSIS	REF. No.	REGRESSION EQUATION	N	r	p
basic halothane 1% fluoromar 6%	carbonic	IV	$Y = -2.28 + 0.34 \times \text{pH}$	28	0.69	p < 0.001
	carbonic	IV	-----	26	-----	n.s.
	carbonic	III	$Y = -3.74 + 0.55 \times \text{pH}$	14	0.61	0.01 < p < 0.05
basic halothane 1%	non-carbonic	V	-----	42	-----	n.s.
	non-carbonic	VI	$Y = 3.11 - 0.39 \times \text{pH}$	28	-0.52	
basic fluoromar 1% fluoromar 3% fluoromar 6%	carbonic	II+III	-----	15	-----	n.s.
	carbonic	II+III	$Y = -2.03 + 0.30 \times \text{pH}$	15	0.56	0.01 < p < 0.05
	carbonic	II+III	$Y = -1.98 + 0.29 \times \text{pH}$	15	0.56	0.01 < p < 0.05
	carbonic	II+III	$Y = -3.0 + 0.44 \times \text{pH}$	15	0.67	0.001 < p < 0.01

Table 5.

RESISTANCE IN THE SPLANCHNIC BED ($\text{kPa l}^{-1}\text{min}$) AS A FUNCTION OF pH

ANAESTHESIA	ACIDOSIS	REF. No.	REGRESSION EQUATION	N	r	p
basic	carbonic	IV	-----	28	--	n.s.
halothane 1%	carbonic	IV	-----	26	--	n.s.
fluoromar 6%	carbonic	III	-----	14	--	n.s.
basic	non-carbonic	V	Y = 235 - 28.8 x pH	42	-0.62	p < 0.001
halothane 1%	non-carbonic	VI	-----	28	--	n.s.
basic	carbonic	II+III	-----	15	--	n.s.
fluoromar 1½%	carbonic	II+III	-----	15	--	n.s.
fluoromar 3%	carbonic	II+III	-----	15	--	n.s.
fluoromar 6%	carbonic	II+III	Y = 681 - 86.0 x pH	15	-0.53	0.01 < p < 0.05

Table 6.

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